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FIFTEEN YEARS' EXPERIENCE WITH FREE FEEDING OF PATIENTS WITH BLEEDING PEPTIC ULCER

Fatal Cases

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FIFTEEN years ago I introduced the "free feeding program" in the treatment of bleeding peptic ulcer, or gross hemorrhage with hematemesis and melena.[1] Since then I have consistently followed the recommendations laid down at that time for the treatment and have repeatedly summarized my material and reported on the results obtained.[2]

The method has been adopted in most countries, and numerous publications dealing with their authors' experiences have appeared. I am unable to give an exhaustive review of the literature on the subject at the present time, particularly with regard to the English and American articles, because, as a result of Denmark's isolation during the war, gaps in the series of periodicals occurred and they have not yet been brought up to date. But as far as I can make out, general agreement on the advantages of the treatment prevails among all those who have had experience with it. There is a consensus that this treatment means an enormous simplification in the care of the patients. Further, they are spared tantalizing discomforts in the form of immobilization, hunger and thirst, and it is therefore much more acceptable to them. It is also agreed that the patients recover more rapidly from hemorrhagic shock, that the general condition quickly improves or at any rate in no way deteriorates and that blood regeneration proceeds at a greater speed. It is also allowed that the tendency to hemorrhage is not increased by food entering the stomach. Some assume that the reason for this is the diminution in the hunger contractions of the stomach. Others connect it with the neutralization of the gastric juice. Whatever the explanation given, that the bleeding is not intensified is accepted as a fact. Some even assert that it is lessened.

From the Medical Clinic B at Bispebjerg Hospital.

1. Meulengracht, E.: Ugesk. f. læger **95**:1257, 1933; Acta med. Scandinav. (supp.) **59**:375, 1934; Klin. Wchnschr. **13**:49, 1934.

2. Meulengracht, E.: Lancet **2**:1220, 1935; Wien. klin. Wchnschr. **49**:1481, 1936; München. med. Wchnschr. **84**:1565, 1937; Brit. M. J. **2**:321, 1939.

It is further agreed that the mortality rate is decreased, which, of course, is the crucial point. However, there is a difference of opinion as to the extent to which it can be lowered. In the United States fairly extensive reports have been published by Nicholson and Miller [3] as well as by Rasberry and Miller.[4] In their collected material, comprising 2,111 cases, they obtained a gross mortality of 4 per cent and a net mortality of 1.9 per cent, the latter figure implying that patients with cancer and perforations and moribund patients who never received the treatment were excluded. Subsequently, Miller's [5] own net mortality figure was only 1 per cent.[5] They set this figure against the mortality rate of 8.7 per cent found by Miller and Elsom [6] among 5,843 patients treated on the old principles of immobilization administration of morphine and starvation (according to Schiff [7] it ought to be 9.1 per cent). The figures, however, vary a good deal from one locality to another, perhaps partly because the number who undergo treatment in a hospital varies extraordinarily in different places.

These records agree fairly well with the Scandinavian figures. Thus when I introduced the treatment in 1931, I found that the mortality rate fell to within 1 to 2 per cent from the 8 to 10 per cent which had previously been the general figure for mortality in Scandinavia for corresponding material treated by the older method (immobilization, administration of morphine and starvation).

It must be pointed out that such a difference would hardly be obtained today. In the course of the later decades, at all events in Denmark, a change in the character of the peptic ulcer has taken place, with the result that the mortality of bleeding peptic ulcer has decreased intrinsically. This question is fully discussed by Alsted [8] in his book, "Changing Incidence of Peptic Ulcer." From this it appears that peptic ulcer has gradually become rarer in women and commoner in men and that the occurrence of gastric ulcer has become less frequent and that of duodenal ulcer more so ("the ulcers have moved down towards the duodenum"). Simultaneously, hemorrhage has become more frequent but possibly less severe. These facts naturally cannot be ignored in a comparison of older material with that of the present day.

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3. Nicholson, I. T. L., and Miller, T. G.: Am. J. Digest. Dis. **8**:446, 1941.

4. Rasberry, E. A., and Miller, T. G.: Gastroenterology **1**:911, 1943.

5. Miller, T. G.: South. Med. & Surg. **107**:54, 1945.

6. Miller, T. G., and Elsom, K. A.: M. Clin. North America **22**:1711, 1938.

7. Schiff, L.: South. M. J. **37**:335, 1944.

8. Alsted, G.: Changing Incidence of Peptic Ulcer, London, Oxford University Press, 1939.

TREATMENT BY PROMPT AND FREQUENT FEEDING

From the first day after their admission to the hospital the patients are given a full "purée diet." The diet includes the following meals: at 6 a. m. tea, white bread and butter, at 9 a. m. oatmeal porridge with milk, white bread and butter, at 1 p. m. dinner, at 3 p. m. milk or cocoa and at 6 p. m. egg, sandwiches, sliced meat, cheese and tea.

The dinner includes a variety of dishes, e.g., different kinds of gruel, porridge, vegetable soups, meat balls, timbale, stewed chops, omelette, fish balls, vegetables au gratin, meat au gratin, fish au gratin, mashed potatoes, vegetable purées, creamed vegetables, stewed apricots, apple sauce and rice and tapioca puddings. The patients are allowed to have as much as they want.

Water and milk are put on the table for free use, and the patients are urged to drink as much as they feel inclined to.

Ferrous tartrate is given in a dose of 0.5 Gm. three times daily. At first alkali and belladonna were also administered, but the use of these is now restricted to patients with cardialgia, which is only rarely present. In severe cases a blood transfusion is given.

It is rather at random that I have chosen the purée diet. One can just as well adopt any other form of bland and nonirritating diet based on the culinary customs of the particular locality. It is more a question of adhering to the principle of something to eat and drink from the first day and a varied and liberal diet given in frequent meals.

MATERIAL UP TO THE PRESENT TIME

In the intervening years since June 1, 1931, when I changed over to the free feeding program as a routine measure, up to June 1, 1946, I have treated a total of 1,031 patients with bleeding gastric ulcer according to these principles. The material comprises 1,005 patients discharged from hospital after completion of the treatment and 26 who died as a near or remote result of the hemorrhage, that is to say, while in hospital.

The 1,031 patients include all those with bleeding gastric ulcer who were admitted to Medical Clinic B at Bispebjerg Hospital in Copenhagen during the period mentioned. This is a municipal hospital, and in Copenhagen hospital conditions are such that practically all patients in whom hematemesis or obvious melena develops are regarded as "nonrejectable" and are admitted immediately.

The material comprises only patients with gross hemorrhage, i.e., distinct hematemesis or directly visible melena. Patients with small quantities of blood in the vomitus ("hematemesis spuria") or with only chemically detectable melena are excluded. Also excluded are patients

who had hemorrhage due to carcinoma of the gastrointestinal tract or to esophageal varicose veins in cirrhosis of the liver or to other diseases which have no connection with peptic ulcers or "ulcer disease." In the case of the discharged patients this was ensured, so far as was possible, with the help of the clinical picture and the course of the disease and in the fatal cases by the fact that a postmortem examination was made of all the patients who died during the period concerned from, or partly from, hematemesis or melena.

There remains then a total number of 1,031 patients, including 26 who died, in whom the hemorrhage was regarded as arising from peptic ulcer or "ulcer disease."

FATAL CASES

The 26 fatal cases were subjected to further investigation.

Sex and Age.—There were 17 men and 9 women, and the age varied from 26 to 86 years. It is worth noting that 25 of the 26 patients were over 40 years of age and half of these were over 60 (table 1).

The patients who died thus belong to the higher age groups.

TABLE 1.—*Distribution of the Patients Who Died According to Age*

Age	Under 40	40 to 50	50 to 60	60 to 70	70 to 80	Over 80
No.	1	6	6	4	7	2

History of Ulcer.—In the investigation of the history it was striking, in view of the fact that at autopsy chronic and often large and deep ulcers were demonstrated, that some of the patients seemed to lack a genuine history of ulcer. Without doubt this was partly because the history was taken on admission of the patients to the hospital, when they had sustained mental or physical shock from hematemesis and loss of blood, with the result that the information was not always absolutely reliable.

Hematemesis or Melena.—In all 26 cases the hemorrhage made its presence known as hematemesis. Usually there was also melena, but some patients did not exhibit this symptom. The hematemesis was most often of a severe type.

The Time of Supervention of Death.—In all 26 cases there was accurate information as to when the bleeding began. In 17 it started immediately before admission to the hospital, that is, within twenty-four hours. In 1 it began eight days, in another ten days and in the remainder a few days before admission. One can thus determine the time which elapsed between the onset of the bleeding and the occurrence of death (table 3).

The result is roughly the same when the duration of the time in hospital until the occurrence of death is considered (table 4).

Pathologic Condition.—On clinical examination a series of complicating diseases was detected. In most cases, however, the investigation was conducted in unfavorable circumstances, and the postmortem examination therefore affords a better basis for determining the condition.

At autopsy as many ulcers were found to be located in the stomach as in the duodenum.

From the pathologic-anatomic standpoint all the ulcers gave the impression of being chronic. Ten were extremely large, reaching the size of up to half the palm of the hand. In 4 patients two or three ulcers were present at the same time. Most of the ulcers in the stomach were penetrating. Three penetrated to the pancreas, one to the pancreas and liver and one to the omentum. In 1 case there was threatened perforation. Of the duodenal ulcers, one had penetrated to the pancreas —resulting in an abscessed cavity in the pancreas and localized fibrinopurulent peritonitis around the stomach—and to the liver and spleen, one had penetrated to the liver and in one the perforation had caused an abscess cavity behind the stomach, which reached downward around the left kidney and upward under the diaphragm and had passed through to the left pleura. Of the jejunal ulcers, one had penetrated to the thoracic wall, while in one there was an open perforation with diffuse purulent peritonitis.

In 17 cases eroded vessels of various sizes were found, most of which appeared to be arteries.

At the autopsies a number of serious complicating diseases were also discovered i.e., arteriosclerosis, fibrosis of the myocardium, cardiac hypertrophy, syphilitic aortitis, aortic aneurysm, pleuropneumonia, embolus of the pulmonary artery, sclerotic kidney and hypertrophy of the prostate.

The Immediate Cause of Death.—The immediate cause of death in the 26 fatal cases is given in table 6.

Two patients died from a large embolus in the pulmonary artery on the sixth and twenty-seventh days respectively after the onset of the hemorrhage and at a time, moreover, when they were improving. The first patient had previously been bedridden on account of prostatic disease. One patient died from diffuse peritonitis following an undiagnosed perforation and 1 from a perforation associated with a large subdiaphragmatic abscess which had infiltrated the tissues and reached the pleura. In 1 hemorrhage and perforation were considered to have had an equal share in causing death, and in another there was extensive lobar pneumonia with a large pleural exudate as well as the hemorrhage.

TABLE 2.—*Data on the Twenty-Six Fatal Cases*

Year	Sex	Age, Years	Duration of Ulcer Symptoms	Manifestation of Hemorrhage	Interval Between First Appearance of Hemorrhage and Admission to Hospital	Interval Between Admission to Hospital and Death	Postmortem Findings	Cause of Death
1931	M	45	6 yr.	Hematemesis and melena	1 day (6 days?)	6 days	Scar on the lesser curvature; gastroenteroanastomosis; perforated peptic ulcer of the jejunum; diffuse purulent peritonitis; stenosis and incompetence of the aortic valves; hypertrophy of the heart; renal sclerosis	Perforation and diffuse peritonitis
1933	M	50	? (moribund)	Hematemesis and melena	2 days	Immediately after admission	Chronic juxtapyloric ulcer; 2 by 2 cm.; walnut-sized abscess in the right lung	Persistent bleeding
1933	M	50	1 yr. (?)	Hematemesis and melena	8 days	17 days	Chronic duodenal ulcer, 3 by 3 cm.; large eroded blood vessel; renal sclerosis; hypertrophy and fibrosis of the myocardium	Repeated bleeding, renal sclerosis and uremia
1934	F	76	1 yr. (?)	Hematemesis and melena	1 day	Within 1 day	Chronic ulcer, 6 by 6 cm.; penetrating to the pancreas; two eroded blood vessels; arteriosclerosis; fibrosis of the myocardium	Persistent bleeding
1936	M	40	2 wk.	Hematemesis and melena	5 days	7 days	Chronic ulcer, 5 by 4 cm., on the lesser curvature penetrating to the pancreas; two or three eroded blood vessels	Persistent or repeated bleeding
1936	F	74	2 yr. (?)	Hematemesis and melena	Within 1 day	6 days	Chronic ulcer, 2 by 2 cm., on the lesser curvature; large eroded blood vessel; arteriosclerosis	Repeated bleeding
1937	M	45	15 yr.	Hematemesis and melena	Within 1 day	1 day	Duodenal ulcer, 3 by 3 cm., penetrating to the pancreas; two or three eroded blood vessels; pyloric stenosis; abscess cavity in the pancreas and fibrinopurulent peritonitis around the stomach, liver and spleen	Persistent bleeding and localized fibrinopurulent peritonitis
1937	M	48	10 yr.	Hematemesis	1 day	7 days	Chronic duodenal ulcer, 1 by 2 cm.; pyloric stenosis	Repeated bleeding
1937	M	86	15 yr.	Hematemesis	Within 1 day	Within 1 day	Chronic ulcer, 5 by 5 cm., just before the pylorus penetrating to the pancreas; large eroded blood vessel; arteriosclerosis	Persistent bleeding
1938	F	59	0	Hematemesis and melena	1 day	1 day	Ulcer of the pylorus, 4 by 6 cm.; eroded blood vessel; mammary carcinoma	Persistent bleeding
1938	M	46	2 mo.	Hematemesis	Within 1 day	2 days	Chronic ulcer, 4 by 4 cm., in the stomach on the posterior wall near the pylorus penetrating to the omentum; large eroded blood vessel; 1 by 1 cm. ulcer in the stomach on the posterior wall	Persistent or repeated bleeding
1938	M	66	19 yr.	Hematemesis and melena	2 days	7 days	Gastroenterostomy with peptic ulcer of the jejunum; eroded blood vessel; chronic bronchitis and emphysema; arteriosclerosis; cardiac hypertrophy; hypertrophy of the prostate	Repeated bleeding
1939	F	69	1 yr.	Hematemesis	Within 1 day	Within 1 day	Chronic ulcer, 1 by 1 cm., in the stomach near the pylorus; eroded blood vessel; syphilitic aortitis; arteriosclerosis; cardiac hypertrophy; nephrosclerosis	Persistent bleeding and cardiac insufficiency

							of the prostate	
1939	F	60	1 yr.	Hematemesis	Within 1 day	Within 1 day	Chronic ulcer, 1 by 1 cm., in the stomach near the pylorus; eroded blood vessel; syphilitic aortitis; arteriosclerosis; cardiac hypertrophy; nephrosclerosis	Persistent bleeding and cardiac insufficiency
1939	M	53	10 yr.	Hematemesis and melena	Within 1 day	9 days	Two small chronic duodenal ulcers; large eroded blood vessel; coronary arteriosclerosis; cardiac hypertrophy	Repeated bleeding
1940	F	82	?	Hematemesis and melena	Within 1 day	2 days	Two small chronic duodenal ulcers; arteriosclerosis; fibrosis of the myocardium	Persistent bleeding
1940	M	73	6 yr.	Hematemesis and melena	8 days	27 days	Chronic ulcer of the pylorus, 2 by 2 cm.; thrombophlebitis of the lower extremities; thrombophlebitis of the inferior vena cava; embolus of the pulmonary artery; fibrosis of the myocardium; renal sclerosis; hypertrophy of the prostate	Embolus of the pulmonary artery
1941	F	68	6 mo.	Hematemesis and melena	2 days	3 days	Chronic ulcer, 5 by 7 cm., on the lesser curvature penetrating to the liver and the pancreas; large eroded blood vessel; large left-sided pleuropneumonia; thrombosis of the pulmonary artery; arteriosclerosis; fibrosis of the myocardium	Pleuropneumonia; repeated bleeding (?)
1942	F	75	2 yr.	Hematemesis and melena	5 days	3 days	Chronic duodenal ulcer, 1 by 1 cm.; eroded blood vessel; arteriosclerosis; fibrosis of the myocardium	Persistent or repeated bleeding
1943	M	57	6 yr.	Hematemesis and melena	Within 1 day	2 days	Chronic ulcer, 1 by 1 cm.; eroded blood vessel	Persistent bleeding
1943	M	47	Many years	Hematemesis	2 days	2 days	Gastroenterostomy; gastrojejunal ulcer penetrating to the abdominal wall; fibrosis of the myocardium; cardiac hypertrophy; renal sclerosis	Repeated bleeding
1943	M	67	25 yr.	Hematemesis and melena	Within 1 day	5 days	Gastroenterostomy; three small chronic duodenal ulcers; large embolus of the pulmonary artery; arteriosclerosis; fibrosis of the myocardium; hypertrophy of the prostate	Embolus of the pulmonary artery
1944	M	26	0	Hematemesis and melena	Within 1 day	10 days	Chronic duodenal ulcer, 2 by 3 cm., eroded blood vessel; syringomyelia	Repeated bleeding
1944	M	76	12 yr.	Hematemesis and melena	Within 1 day	2 days	Chronic duodenal ulcer, 2 by 2 cm.; eroded blood vessel; arteriosclerosis	Persistent bleeding
1944	M	58	2 yr. (?)	Hematemesis and melena	10 days	12 days	Chronic duodenal ulcer, 4 by 5 cm., penetrating to the liver; large eroded blood vessel; syphilitic aortitis; aortic aneurysm	Repeated bleeding
1944	F	71	Several years	Hematemesis and melena	Within 1 day	5 days	Ulcer, 1 by 1 cm., on the lesser curvature, with threatened perforation; eroded blood vessel; arteriosclerosis; cardiac hypertrophy; fibrosis of the myocardium	Repeated bleeding and cerebral thrombosis
1945	F	78	30 to 40 yr.	Hematemesis and melena	Within 1 day	3 days	Gastroenterostomy; 5 by 5 cm. and 1 by 1 cm. chronic ulcers on the lesser curvature; 1 by 1 cm. chronic duodenal ulcer perforating to a large abscess cavity; the abscess lies behind the stomach and extends upward under the diaphragm and downward to the left kidney, and there is passage through to the left pleura; arteriosclerosis; fibrosis of the myocardium	Perforation and subdiaphragmatic abscess

Hemorrhage and cerebral thrombosis, with complete hemiplegia, were thought to be equally responsible for 1 death.

In 19 cases the hemorrhage itself was regarded as the immediate cause of death. In about half these it was thought that there had been persistent hemorrhage and in the other half repeated hemorrhage. In this decision, the length of time which had elapsed since the onset of the bleeding and the question of whether there had been clinical signs

TABLE 3.—*Interval Between Onset of Bleeding and Occurrence of Death*

Days	0 to 2	2 to 5	5 to 10	Over 10
Number of patients	5	8	8	5

TABLE 4.—*Interval Between Admission to Hospital and Occurrence of Death*

Days	0 to 2	2 to 5	5 to 10	Over 10
Number of patients	5	8	8	5

TABLE 5.—*Location of the Ulcers in the Twenty-Six Fatal Cases*

Locus	Number
Stomach	9
Pylorus	2
Duodenum	11
Stomach and duodenum	1
Gastroenterostomy opening	3

TABLE 6.—*Immediate Cause of Death in the Twenty-Six Fatal Cases*

Embolus of the pulmonary artery	2
Perforation and peritonitis	2
Bleeding and perforation	1
Bleeding and pleuropneumonia	1
Bleeding and thrombosis (hemorrhage?) of the brain	1
Persistent bleeding	9
Repeated bleeding	10

of a fresh hemorrhage were taken into consideration. It must be admitted that it was frequently difficult to distinguish between persistent and repeated hemorrhage.

It was apparent that a number of factors had lessened the patients' capacity for resistance. Nine were over 70 years of age and exhibited, more or less, the general weakness associated with old age. Arteriosclerosis was present in 12 and fibrosis of the myocardium in 10. One had syphilitic aortitis, 1 syphilitic aortitis and aortic aneurysm, 1 chronic purulent bronchitis and emphysema, 1 a small pulmonary abscess, 5

compensatory sclerosis of the kidneys and 1 noncompensatory sclerosis of the kidneys and uremia. Even if these conditions in themselves would not have caused death at the stage in question, it is clear that their presence rendered the patients less able to withstand the hemorrhage.

Mortality.—If the number of patients who died from, or partly from, the hemorrhage, i.e., while in hospital, is to be calculated, the figures 1,031 and 26 must be used, and a gross mortality of 2.5 per cent is obtained.

If patients are excluded whose deaths were entirely or in the main due to causes other than bleeding (embolus of the pulmonary artery, 2 patients; perforation and peritonitis, 2 patients; pleuropneumonia, 1 patient; thrombosis [hemorrhage ?] of the brain, 1 patient) as well as those who died within twenty-four hours of admission (one, eight, fifteen, twenty-two and twenty-three hours respectively) and had therefore not received the treatment, a net mortality of 1.5 per cent is obtained.

COMMENT

An analysis of the fatal cases discloses that there was a definite preponderance of deaths in the older age groups. The average age of the 26 patients was 57 years; 96 per cent were over 40 and 50 per cent over 60. In contrast to this, the majority of the patients in my collected material belong to the lower age groups. In an earlier study (1935) Rischel found an average age of 48 years; 66 per cent were over 40 and 23 per cent over 60.

This therefore signifies that the risk of hemorrhage in the free feeding program is greatest in the higher age groups, which is presumably due to the poor condition of the vessels and the various complicating diseases in those age groups. In patients under 40 years of age the risk is clearly slight. The same risk in the higher age groups is present also with other forms of treatment. Hansen and Pedersen [9] thus found that of 393 patients with fatal hematemesis and melena in Copenhagen hospitals during the period 1915 to 1937, 87 per cent were over 40 years of age, and the largest number of deaths involved patients 60 to 69 years of age.

In all the fatal cases the bleeding manifested itself as hematemesis. The frequency of hematemesis was far greater among the fatal cases than in my collected material. Rischel [10] noted hematemesis one hundred and twelve times and melena ninety-four times. In extensive collected material from Copenhagen hospitals during the period 1925 to 1935 Alsted [8] found that in 684 cases the bleeding had manifested itself as melena. Since then there has been a change in the direction of the still rarer occurrence of hematemesis.

9. Hansen, J. L., and Pedersen, J.: Nord. med. **7**:1567, 1940.

10. Rischel, A.: Klin. Wchnschr. **15**:335, 1936.

This therefore means that hematemesis indicates a worse prognosis than melena. The presence of hematemesis does not depend so much on the site of the ulcer as on the fact that the more sudden and profuse the hemorrhage the greater is the probability that it will manifest itself as hematemesis (Pedersen [11]). In conformity with this statement, in nearly all the fatal cases in which the bleeding was considered to be the immediate cause of death large eroded vessels were seen at the postmortem examination.

That hematemesis indicates a worse prognosis than melena is also found with other forms of treatment. Thus Hansen (cited by Pedersen [11]) in a collected material of 97 fatal cases of bleeding peptic ulcer from the Municipal Hospital of Copenhagen during the period 1915 to 1935, found that in 85 the hemorrhage had manifested itself as hematemesis.

At the autopsies, nine gastric as compared with eleven duodenal ulcers were found. This is a greater number of gastric ulcers than that which occurs in the clinical material. Thus Alsted found about five times as many duodenal as gastric ulcers. The gastric ulcers clearly had a greater tendency to fatal hemorrhage.

In settling what shall be regarded as gross mortality and what is net mortality, one can naturally establish different criteria. In calculating my gross mortality of 2.5 per cent, I have included all the deaths if they occurred while the patients were in hospital. In calculating my net mortality of 1.5 per cent, I have excluded deaths due to causes other than hemorrhage and deaths which occurred so soon that the patients had not received the treatment. The justification for excluding the latter can of course be contested, but with a view to comparison I have proceeded on the same lines as Miller and others,[12] by which they obtained the figures 4 per cent and 1.9 per cent [1] for gross and net mortality respectively.

Although it may now be said to have been proved that the free feeding program gives lower mortality figures and although Miller [13] in my opinion expresses it accurately when he says that "to the average case the prompt feeding program offers the best chance for survival," it may nevertheless be in order to inquire whether the treatment in the fatal cases has not only been useless but has even done harm.

It must be pointed out to begin with that in a large number of the fatal cases the patients did not get any treatment at all. Thus 5 patients died shortly after their admission to the hospital, and they moreover were so ill that they could neither eat nor drink. Eight died in the

11. Pedersen, J.: Nord. med. **9**:252, 1941.

12. Nicholson and Miller.[3] Rasberry and Miller.[4]

13. Miller, T. G.: Ann. Int. Med. **15**:390, 1941.

course of two to five days. They were also so ill that it was difficult to get them to eat or drink anything. Even those who died in five to ten days took little fluid or nourishment. Time after time in the clinical histories of the fatal cases there appears the statement that the patients were so ill that they could neither eat nor drink or that it was difficult to get them to do so. That is the tragic part of it; for these patients, in a still greater measure than those with less severe illness, need all the support which they can get. In my view, therefore, it can be said that in these cases it is not the treatment that has done harm but the lack of it.

Could some of the patients have been saved by operation with a view to hemostasis? Against this it should be pointed out in the first place that it would have been difficult to dissociate these 26 patients from the total number, at any rate before they had become extremely ill or even before they had become almost moribund. Further, a more detailed clinical and postmortem analysis of the 26 patients shows that practically all of them would have been bad subjects for a resection operation. On admission to the hospital all were suffering from a severe state of shock and debility and some were moribund. Half of them were over 60 years of age, and the oldest was over 83. In many there were complicating diseases, e. g., arteriosclerosis, cardiac fibrosis or renal sclerosis. Many had large ulcers penetrating to the pancreas or liver; extensive resections would have been necessary. In 6 the cause of death was something other than hemorrhage. In actual fact there were only a few for whom, seen in review, one felt that there might have been a reasonable chance that they would tolerate resection. My own view up to now has been that a patient with bleeding gastric ulcer should not be transferred for operation during or just after a hemorrhage, and perusal of the fatal cases in my own material has rather served to strengthen me in this opinion even if I admit that there might be a few cases in which operation might be lifesaving. A gross mortality of 2.5 per cent and a net mortality of 1.5 per cent seem to be satisfactory under the conditions. There must always be a certain basal mortality.

Yet it is not impossible that these figures could be reduced still further. Modern surgery teaches how enormously the prognosis in a number of operations has been improved by the introduction of systematic control of the patient's hemoglobin, plasma protein and water and electrolyte balance, with the readjustment of any deficit by means of blood transfusions and the parenteral administration of dried serum, dextrose solution and isotonic solution of sodium chloride or isotonic solution of bicarbonate before or, particularly, after the operation. There is no doubt in my mind that patients with bleeding gastric ulcer should be on a par with patients operated on; they are suffering from post-

hemorrhagic shock, and much risk can be obviated by making good, as far as possible, the deficit of hemoglobin, plasma protein, water and salts which exists. This is one of the things which the free feeding program aims at through the liberal supply of food and drink. When I now reflect on my fatal cases, I admit that I employed blood transfusion on far too small a scale, and from now on I shall arrange for the systematic control of cases which threaten to terminate fatally as well as for the more ample use of blood transfusions. According to investigations from Witt's clinic by Black and Smith,[14] the use of dried serum cannot be advised as it compares unfavorably with whole blood and may have ill effects.

If in the future I should consider the advisability of operation, it shall be, as seen from the perusal of my fatal cases, in instances in which the patient is more than 40 years of age, has persistent or repeated bleeding, manifesting itself as hematemesis, and threatens to die in spite of repeated blood transfusions. There should be no serious contraindications to operation, the presence of an ulcer should have been proved by roentgenologic study and a good surgeon should be available.

SUMMARY

1. Results are reported from fifteen years of the systematic use of free feeding in bleeding peptic ulcer, with special regard to mortality.

2. The treatment has been used as a routine measure in a total of 1,031 consecutive cases of bleeding peptic ulcer.

3. Of the 1,031 cases, 26 terminated fatally during the patient's stay in the hospital.

4. In all the fatal cases except 1 the patients were more than 40 years old. Many had large ulcers penetrating to the pancreas or the liver, and many had complicating diseases.

5. If all the fatal cases are included, the gross mortality is 2.5 per cent. If cases are excluded in which death was entirely or mainly due to causes other than bleeding as well as those in which the patients died twenty-four hours after admission to the hospital and therefore before they had received the treatment, the net mortality is 1.5 per cent.

6. A more ample use of blood transfusions is recommended in cases which threaten to terminate fatally.

14. Black, D. A. K., and Smith, A. F.: Brit. M. J. **1**:187, 1941.

EPIDEMIOLOGIC STUDY OF SEVEN HUNDRED AND FIFTY-SEVEN CASES OF RHEUMATIC FEVER

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NEW HAVEN, CONN.

DURING World War II rheumatic fever was one of the major causes of lost man days due to sickness in the Navy and Marine Corps. Coincident with large epidemics of hemolytic streptococcus infections which occurred in all the large naval training centers during the years 1942 to 1945 inclusive, the incidence of rheumatic fever rose to epidemic proportions by 1943 and the incidence of valvular heart disease increased accordingly. The number of cases of rheumatic fever in the Navy rose from 148 in 1940 to 7,668 in 1944. The rate per thousand persons increased during the same period from 0.73 to 2.29. The magnitude of the problem of rheumatic fever necessitated the establishment of two naval hospitals for the care of patients with this disease. Likewise, the Army experienced epidemics of hemolytic streptococcus infections as well as a sharp increase in the rate of rheumatic fever. However, the rate of rheumatic fever in the Army was much lower than that in the Navy. Table 1 gives a comparative picture of the rates of rheumatic fever in the Army and Navy and the total number of cases. Table 2 shows that the number of sick days from rheumatic fever in the Navy rose from 12,903 in 1940 to 1,307,475 in 1944. Table 3 points out a similar increase for diseases of the mitral valve from 1940 to 1944.

Rheumatic fever was not among the first ten causes of sick days in the Navy in 1940, but by 1944 it had risen to second place, outnumbered only by simple fractures. Table 4 shows the diseases and noncombat injuries responsible for the greatest number of lost man days in the Navy and Marine Corps from 1940 to 1945.

It is interesting to note that the rate of incidence of rheumatic fever for both the Army and the Navy is considerably less for World War II than for World War I. Most of the cases of rheumatic fever occurred, however, in the training centers, and here the rate far exceeded that

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From the United States Naval Hospital, Dublin, Ga.

This work was done while the author was on active duty as an officer in the United States Naval Reserve.

The Bureau of Medicine and Surgery does not necessarily endorse the views and opinions expressed in this article.

for the Navy as a whole, although exact figures are not available. Also it is highly probable that the rate for the training centers exceeded that for the civilian population.

Although of no epidemiologic importance, it seems worth while to comment that the final chapter in the illness of the men who acquired rheumatic fever in the armed forces has not been written; they have many days of sickness ahead of them. From the studies of Jones and Bland [1] and Hedley [2] it can be predicted that many of these men will have impaired ability for activity and that the life expectancy of the

TABLE 1.—*Number of Cases of Rheumatic Fever and Rate per Thousand in the Army and Navy for World War I and World War II* *

Year	Number of Cases		Rate per 1,000	
	Army	Navy	Army	Navy
1917	5,423	1,057	7.99	4.30
1918	18,020	2,772	7.16	5.50
1919	1,923	.....	1.91	....
1940	122	148	0.36	0.73
1941	1,113	489	0.83	1.40
1942	1,649	868	0.51	1.04
1943	7,426	5,808	1.08	2.75
1944	5,731	7,668	0.72	2.29
1945	3,675	6,461	0.52	1.76

* The Surgeon General's report (Army) for the period of World War I, April 1, 1917 to Dec. 30, 1919 inclusive, gives for acute articular rheumatism a total of 24,770 cases, with an incidence rate of 6.00 per thousand persons per annum. The incidence of rheumatic fever (Army) in each year of the period 1941 to 1945 is considerably in excess of that in the Army's prewar experience. For several years immediately preceding the war the rate varied between 0.8 and 0.36 per thousand per annum.

TABLE 2.—*Rheumatic Fever in the Navy and Marine Corps in 1940 to 1945*

Year	Number of Cases	Days of Sickness
1940	148	12,903
1941	489	35,215
1942	868	62,952
1943	5,808	472,708
1944	7,668	1,307,475
1945	6,461	1,245,380

group as a whole will be shortened. Seventy-five (21.5 per cent) of 349 patients included in this group and studied separately by Lt. Comdr. T. W. Steege already had valvular heart disease at the time of discharge.[3]

Rheumatic fever is of extreme importance as a world health problem, and few facts are known concerning its epidemiology, etiology and pathogenesis. Because of the Navy Medical Corps's wide experi-

1. Jones, T. D., and Bland, E. F., Jr.: Rheumatic Fever and Heart Disease: Completed Ten-Year Observation on 1,000 Patients, Tr. A. Am. Physicians **57**:267, 1942.

2. Hedley, O. F.: Mortality from Rheumatic Heart Disease in Philadelphia During 1936, Pub. Health Rep. **52**:1907 (Dec. 31) 1937.

3. Steege, T. W.: Unpublished data.

ence with this disease, it is considered of value to report a study of the epidemiologic pattern in rheumatic fever in a group of enlisted personnel in the Navy and Marine Corps in order to add to the general fund of information of factors which set the stage for this disease.

DESCRIPTION OF STUDY GROUP AND METHODS

The patients under consideration in this study were admitted to the United States Naval Hospital at Dublin, Ga., between March 15, 1945 and March 15, 1946. There were 1,470 patients admitted for rheumatic fever during this period, and 757 of these patients, all enlisted

TABLE 3.—*Incidence of All Diseases of the Mitral Valve in the Navy and Marine Corps in 1940 to 1944*

Year	Number of Cases	Days of Sickness
1940	60	3,677
1941	306	14,538
1942	775	31,203
1943	1,991	85,153
1944	1,856	122,440

TABLE 4.—*Diseases and Noncombat Injuries Responsible for the Greatest Number of Lost Man Days in the Navy and Marine Corps in 1940 to 1944* *

Year	Greatest Amount of Lost Time	Per Cent of Total	Next Greatest Amount of Lost Time	Per Cent of Total	Third Greatest Amount of Lost Time	Per Cent of Total
1940	Catarrhal fever, acute	8.89	Gonococcic infection, urethra	8.62	Appendicitis, acute	3.51
1941	Catarrhal fever, acute	7.55	Gonococcic infection, urethra	4.30	Appendicitis, acute	3.47
1942	Catarrhal fever, acute	8.67	Gonococcic infection, urethra	3.89	Appendicitis, acute	3.37
1943	Malaria, all forms	8.48	Gonococcic infection, urethra	6.05	Fracture, simple	3.96
1944	Fracture, simple	4.07	Rheumatic fever	3.68	Catarrhal fever, acute	3.43

* The data in this table are taken from the medical statistics of the United States Navy. The percentages are based on the total days of sickness for all diseases and noncombat injuries.

male personnel of the Navy and Marine Corps, comprise the study group. The hospital is one of two established by the Navy as centers for the treatment of rheumatic fever, and patients were transferred to it principally from other naval hospitals east of the Mississippi River.

The majority of the patients were interviewed for this study after they had been in the hospital at least two months.

OBSERVATIONS

1. *Location of the Patient's Home and the Number and Per Cent by States Who Had Rheumatic Fever Before Enlistment.*—The community in which the patient had lived during his childhood and early adulthood

coincided in at least 95 per cent of the cases. The majority of patients came from homes east of the Mississippi River and were stationed in this same area at the time of the onset of their present illness.

The number who were known to have had rheumatic fever prior to enlistment was determined by a careful taking of the history, and by the time the patients were interviewed a past history of rheumatic fever had been established or ruled out. Furthermore, it was the policy of the medical survey board at the hospital to discharge all persons from the service who had had more than one attack of rheumatic fever. The validity of the first attack was considered carefully by the survey board, and in most cases a letter from the patient's family physician gave further proof of earlier illness. The patient was not considered to have had a previous attack of rheumatic fever unless there was clearcut supporting evidence.

In table 5 the home states of 754 of the patients are grouped according

TABLE 5.—*Location of Home of Patients with Rheumatic Fever*

Geographic Area, States	Number of Patients	Number with Rheumatic Fever Before Enlistment	Per Cent with Rheumatic Fever Before Enlistment
New England	87	21	24.1
Middle Atlantic	197	56	28.4
South Atlantic	160	42	26.2
South Central	77	10	12.9
North Central	211	51	24.1
Plateau	8	1	12.5
Pacific	14	4	28.5

to geographic areas. The North Central states contributed the highest number, 211 men, and of this number 51 (24.1 per cent) gave a history of rheumatic fever prior to enlistment. In the Middle Atlantic states there were 197, with 56 (28.4 per cent) giving a history of previous rheumatic fever. In the South Atlantic states there were 160, with 42 (26.2 per cent) having had the disease before. In the New England states the corresponding figures were 87 and 21 (24.1 per cent); from the South Central states there were 77, of whom 10 (12.9 per cent) had had previous rheumatic fever, and from the Pacific states there were 14, 4 of them (28.5 per cent) with a past history of the disease. The smallest group, 8, were from the plateau states, and only 1 of these (12.5 per cent) had a history of previous rheumatic fever.

Exact figures were not determined for the entire group, but at least 75 per cent came from urban homes.

Comment: It is not intended that these figures should give any estimate of the incidence of rheumatic fever in the respective geographic areas; they merely indicate that the disease is present in all these regions. A majority of patients grew up in urban areas, and a large per cent

(24.5) had rheumatic fever prior to enlistment. The comparatively large numbers of men with previous rheumatic fever who came from homes in the New England, Middle Atlantic, North Central and South Atlantic states indicate that the disease is widespread in these sections. The high per cent of men from Florida, Georgia, Mississippi and North and South Carolina who had the disease in childhood is no index of the true incidence of rheumatic fever in these states but does lend weight to the idea that the disease is not uncommon in these areas. A recent investigation of the incidence of rheumatic fever in school children in Dublin, Ga., bears out this observation.[4]

2. *Age at Onset of Rheumatic Fever.*—The age of the patient at the time of his first recognized attack of rheumatic fever and the number of patients who apparently acquired the disease at this age are shown in

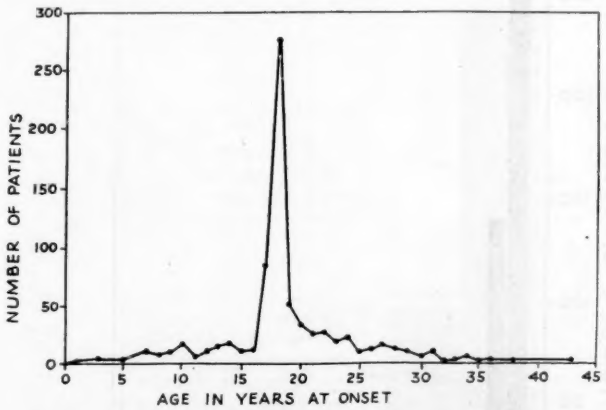

Fig. 1.—Age of patients at the time of the onset of rheumatic fever.

figure 1. The youngest age at the time of onset was 1 year, and the oldest was 43. Seven patients had their first attack of rheumatic fever between the ages of 1 and 5 inclusive, 50 between the ages of 5 and 10, 69 between the ages of 11 and 16 and 412 between the ages of 17 and 19 inclusive. Seventeen is the minimum age for enlistment in the Navy and Marine Corps. The onset occurred in 139 patients when they were between the ages of 20 to 26 inclusive, and in 55 the disease made its initial appearance when they were between 26 and 30. Twenty-five had rheumatic fever for the first time between the ages of 31 and 43 inclusive.

A percentage analysis of figure 1 reveals that 0.9 per cent of the total group of 757 acquired rheumatic fever between the ages of 1 and

4. Quinn, R. W.: The Incidence of Rheumatic Fever and Heart Disease in School Children in Dublin, Georgia, Am. Heart J. **32**:234 (Aug.) 1946.

5 inclusive, 6.6 per cent between 5 and 10, 9.1 per cent between 10 and 16, 54.4 per cent between 17 and 19, 18.4 per cent between 20 and 25, 7.3 per cent between 25 and 30 and 3.3 per cent between 31 and 43.

3. *Ages of Patients Comprising the Study Group.*—The Patients' ages ranged from 17 to 43 (fig. 2). As might be expected, the youngest age groups accounted for the majority of patients, 460 (61.1 per cent) being from 17 to 19. The largest number of patients, 279 (36.9 per cent), were 18 years of age. The number of patients decreased

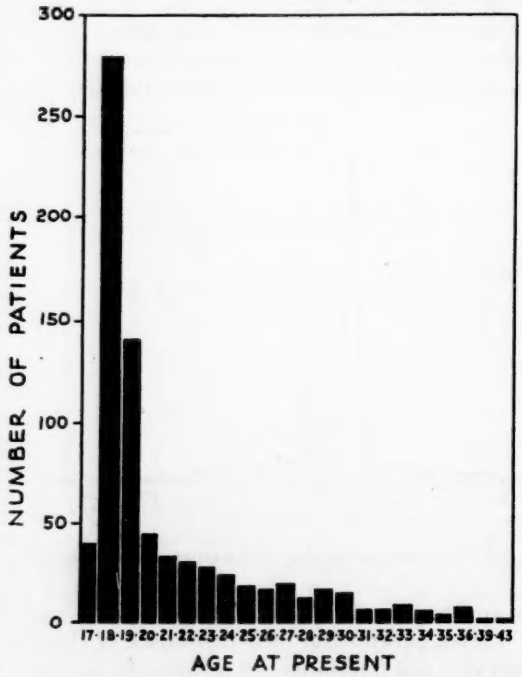

Fig. 2.—Age of the patients in the study group.

gradually in the older age groups; there were 45 who were 20 years of age and only 1 each at the age of 39 and 43.

Comment: The age at the first attack of rheumatic fever in the largest number of this group is considerably older (17 to 19) than the age of onset for persons in the civilian population as a whole (7 to 10).[5] One point of view in relation to rheumatic fever is that it practically always has its onset in childhood, but in the majority of

5. Armstrong, D. B., and Wheatley, G. M.: Studies in Rheumatic Fever, Metropolitan Life Insurance Company, November 1944.

the cases under study the disease apparently made its initial appearance after the men had reached young adulthood. This of course gives a considerably different picture from that given by the statistics on age at first attack of rheumatic fever gathered in hospital clinics. It is well known that there are many persons with valvular heart disease who give no past history of rheumatic fever, perhaps 40 per cent; also it is possible that some of these patients actually did have rheumatic fever in childhood which was unrecognized. This present study emphasizes further that under conditions which exist in the Navy training centers rheumatic fever becomes a disease of young adults.

4. *Number of Attacks of Rheumatic Fever per Patient Before and After Enlistment.*—One hundred and eighty-five patients (24.5 per

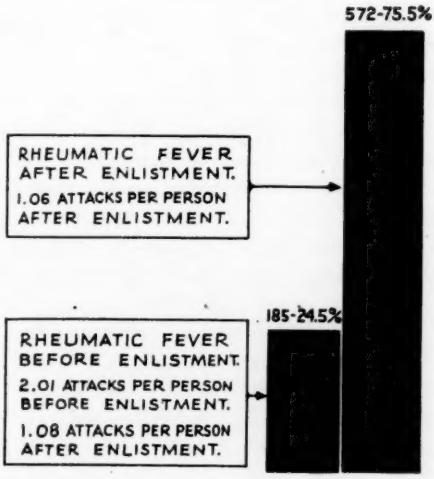
572-75.5%
RHEUMATIC FEVER AFTER ENLISTMENT.
1.06 ATTACKS PER PERSON AFTER ENLISTMENT.
185-24.5%
RHEUMATIC FEVER BEFORE ENLISTMENT.
2.01 ATTACKS PER PERSON BEFORE ENLISTMENT.
1.08 ATTACKS PER PERSON AFTER ENLISTMENT.

Fig. 3.—Number of attacks of rheumatic fever per patient before and after enlistment.

cent) gave a definite history of rheumatic fever before enlistment in the Navy or Marine Corps. The total number of previous attacks in these patients was 373 (2.01 attacks per person). The number of previous attacks per person varied widely, 105 having had one attack and 1 patient estimating that he had experienced fifteen separate bouts before enlistment.

Five hundred and seventy-two patients (75.5 per cent) had never had rheumatic fever prior to enlistment in the Navy or Marine Corps. Of this number, 538 had one attack, 21 had two attacks, 4 had three attacks and 1 had four attacks after enlistment. These data are given in figure 3.

The 572 patients who did not have the disease before enlistment had a total of six hundred and twelve attacks (1.06 attacks per person) after enlistment, whereas the 185 with previous rheumatic fever had two hundred attacks (1.08 attacks per person) after enlistment. A total of eight hundred and twelve attacks of rheumatic fever after enlistment occurred in the study group (1.07 attacks per person).

Comment: One fourth of the patients had rheumatic fever prior to enlistment. This figure is smaller than that found by Manchester in his study of rheumatic fever in naval personnel.[6]

The number of attacks per person after enlistment was approximately the same for patients with as for those without previous experience with rheumatic fever. Possibly those who acquired rheumatic fever in the Navy are just as susceptible to the disease as the group who had it previously when conditions favoring its onset are present.

5. *Geographic Location and Duty Status of Patients at the Time of Onset of Illness.*—Geographic Location (table 6): Six hundred and thirty-one men had their present attack of rheumatic fever within the continental limits of the United States. The great majority (531 or 70 per cent) acquired their illness in five states, Illinois, Maryland, New York, Rhode Island and Virginia. Large numbers of men were stationed in these states. Boot camps and service schools were located at Sampson, N. Y., Bainbridge, Md., and Great Lakes, Ill. A construction battalion training camp was located in Rhode Island, and many service schools and naval establishments were in the vicinity of Norfolk, Va. Thirty-three men were on foreign shore duty when their illness began, 6 being in North Africa, 5 in England and 22 in the Pacific area, which included the territory of Hawaii and the South-West and Central Pacific. Ninety-three became ill while on sea duty, 40 while their ship was in port and 53 while at sea. Of the 40 whose illness began in port, 27 were in United States ports, chiefly along the east coast in New York, Boston and Norfolk, 2 were in England, 7 were in Pacific ports (not in the United States), 2 were in Mediterranean ports, 1 was in a North African port and 1 was in Normandy, France. Nineteen of those stricken at sea were in the Atlantic (17 in the North Atlantic), 32 were in the Pacific (at least 27 in the South West Pacific), 2 were in the Panama Canal Zone and 1 was in the Gulf of Mexico.

Duty Status (table 6): The duties of those who became ill within the continental limits of the United States can be divided into four classes: Two hundred and seventy-four were in boot training; 160 were in service schools such as gunnery or radar schools or schools for radio technicians; 101 were on general duty, which included any of the duties of the rated or nonrated men such as the boatswain's mate, pharmacist's

6. Manchester, R. C.: Rheumatic Fever in Naval Personnel, Arch. Int. Med. 66:317 (March) 1946.

mate, seaman or fireman, and 96 were in outgoing units, awaiting transfer to a station for new duty. Approximately three-fourths of this group had just completed boot training. Their duties consisted mainly in deck, cleaning, "head" and galley details.

All patients who became ill on a foreign shore had duties of rated or nonrated personnel, and there was nothing unusual, from an epidemiologic standpoint, about their work. Patients who became ill while on sea duty, either in port or at sea, were for the most part members of a ship's company. Their duties were those of any enlisted personnel,

TABLE 6.—*Geographic Location and Duty Status of Patients at the Time of Onset of Rheumatic Fever in the Service*

Location	General Duty	Outgoing Unit	Boot Training	Service School	Total
Continental United States	101	96	274	160	631
Foreign shore duty					
North Africa	6	..	...	...	6
England	3	2	...	...	5
Pacific area	20	2	...	...	22
Total	29	4	...	...	33
Sea duty in port					
United States	27	..	...	...	27
England	2	..	...	...	2
Pacific	7	..	...	...	7
Mediterranean	2	..	...	...	2
France	1	..	...	...	1
North Africa	1	..	...	...	1
Total	40	..	...	...	40
Sea duty at sea					
Atlantic	19	..	...	...	19
Pacific	31	..	...	...	31
Panama Canal	2	..	...	...	2
Gulf of Mexico	1	..	...	...	1
Total	53	..	...	...	53
Totals	223	100	274	160	757

such as those of the signalman, deck hand or fire control man, but the majority were nonrated men.

Comment: The prevalence of rheumatic fever in the Navy and Marine Corps as a whole is not high. This suggests that the Navy and Marine Corps provide healthy occupations as far as rheumatic fever is concerned. However, in war years epidemics of rheumatic fever occur. The highest rate is found in the recruit training centers and service schools of the Navy. These establishments were located in New York, Rhode Island, Maryland, Illinois and Idaho, where annual death rates from rheumatic fever in white persons aged 5 to 24 years for the years 1939 to 1941 were extremely high.[5] This suggests that the sections where training centers and service schools are located favor a high rate of rheumatic fever. In a small number of cases the disease appeared in men while in tropical or subtropical zones.

In general, the duties of the men in the study groups were not different from those of enlisted personnel in the Navy or Marine Corps who did not get rheumatic fever. It cannot be said that the duty status of the patients revealed anything of epidemiologic importance, although it has been stated by some that the strenuous activities of trainees, which are attended by excessive fatigue, make them more susceptible to infectious disease.

6. *Length of Time on Active Duty Before the Onset of Rheumatic Fever.*—Figure 4 shows the number and per cent of patients who acquired rheumatic fever during each three month period after going on active duty. Three hundred and six (40.4 per cent) acquired rheumatic fever during the first three months of active duty. One hundred and

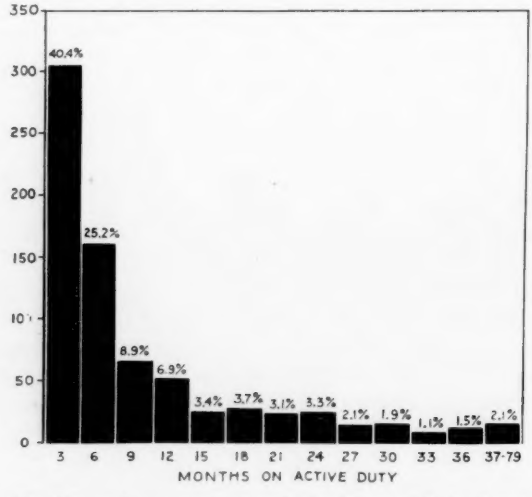

Fig. 4.—Number and per cent of patients who acquired rheumatic fever in each three month period after entry into the navy.

sixty-one became ill during the second three month period. Sixty-seven (8.9 per cent) and 52 (6.9 per cent) became ill during the third and fourth three month periods. A total of 586 (77.4 per cent) acquired rheumatic fever during their first year in the Navy, 103 (13.6 per cent) during the second year, 52 (6.9 per cent) during the third year and only 16 (2.1 per cent) from the thirty-seventh to the ninety-seventh month inclusive.

Comment: It is significant that 77.4 per cent of the men acquired rheumatic fever during the first year of their "Navy life." This number is remarkably close to the observations of Manchester [6] and Coburn.[7]

7. Coburn, A. F.: The Management of Navy Personnel with Rheumatic Fever, U. S. Nav. M. Bull. **41**:1324 (Sept.) 1943.

Even more significant is the fact that 79.6 per cent of the group who acquired the disease in their first year in the Navy became ill within the first six months. However, in the light of past experience this course of events might have been expected. Massing of troops has always been attended by an increase in the incidence of disease,[8] and it has been said that the first months of life in the armed services are as dangerous to the recruit, from the standpoint of disease, as the first years of life for the infant.[9] On the other hand, only a small number of seasoned men were stationed at training centers or service schools, and for this reason it can only be guessed what would have happened to older seasoned men in circumstances similar to those affecting trainees.

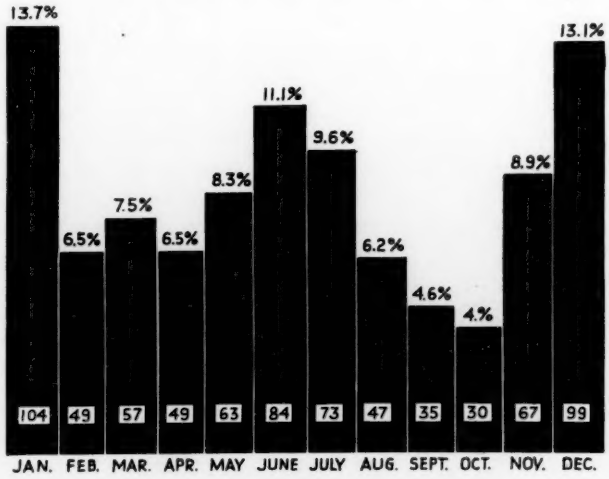

Fig. 5.—Month of onset of rheumatic fever and number and per cent of patients who acquired rheumatic fever in each month.

7. *Month of Onset of Present Illness.*—Figure 5 shows the number and per cent of the total group who became ill each month. (It is self explanatory and needs no particular description.)

Comment: The figure is not meant to give a picture of the seasonal trend of rheumatic fever in the Navy. It merely illustrates the fact that rheumatic fever can and did occur at any season.

8. *Types of Infection Which Preceded the Onset of Rheumatic Fever.*—The types of infection which preceded the onset of rheumatic fever are listed in table 7. Five hundred and forty-five patients (71.9 per

8. Hale, R. A.: Epidemiology in Mobilization, Mil. Surgeon **82**:243 (March) 1938.

9. Boudreau, F. G.: Epidemic Hazards in War, New York State J. Med. **40**:1089 (July 15) 1940.

cent) had a definite infection of the upper respiratory tract preceding the onset of the rheumatic syndrome. The clinical diagnoses given to these infections were in the following order of frequency: catarrhal fever, tonsillitis, pharyngitis, laryngitis, sinusitis and bronchitis. The term catarrhal fever as used by the Navy does not designate a specific disease but is used to classify nonspecific febrile illnesses of the upper respiratory tract. Undoubtedly, in many cases of hemolytic streptococcus infections the diagnosis of catarrhal fever was made. One hundred and seven (14.1 per cent) of the patients had scarlet fever before their rheumatic fever. Unusual infections or illnesses preceded the rheumatic syndrome in 18 (2.4 per cent) patients. Of this number, 2 had dysentery, 1 appendicitis and 9 pneumonia; 3 had teeth extracted, 1 had an abscess of the finger, 1 had fever of unknown cause and 1 had had cholera immunization prior to his illness. It was difficult to establish accurately the length of time between the onset of the infection of the upper respiratory tract and the onset of symptoms of rheumatic fever, but the extreme limits were around two days and two months. Most of the patients dated the onset of their illness with the beginning of

TABLE 7.—*Type of Infection Which Preceded Rheumatic Fever*

	Number	Per Cent
Infection of the upper respiratory tract (catarrhal fever, tonsillitis, pharyngitis, laryngitis, sinusitis, bronchitis)	545	71.9
Scarlet fever	107	14.1
Unusual infections or events	18	2.4
No preceding infection	76	10.0

pain in the joints. A few stated that their sore throat did not start until after they had noticed pain and swelling in the joints. It should be pointed out that rarely was it possible to determine from the record of the patient's health the infecting organism associated with the infection of the upper respiratory tract which preceded the rheumatic syndrome. However, most of the patients were stationed at naval establishments in which hemolytic streptococcus infections were epidemic; also, the clinical manifestations of their respiratory infections were similar to those in patients with known hemolytic streptococcus infections.

In a consideration of the experience of the Navy as a whole, table 8 clearly shows the rise in the rate of rheumatic fever from 1940 through 1943 as infections of the upper respiratory tract and scarlet fever increased. It is impossible to know how many of the infections diagnosed as catarrhal fever actually were hemolytic streptococcus infections; a conservative estimate might be 50 per cent. Acute pharyngitis, acute tonsillitis and scarlet fever probably were all caused by the hemolytic streptococcus. These infections do not represent the total number of strepococcic infections for the years mentioned, because there

were many thousands of cases of laryngitis, sinusitis and rhinitis in which the condition was undoubtedly caused by this organism.

In the present study group 76 patients (10 per cent) had no infection of the upper respiratory tract preceding their rheumatic fever of which they had been aware. An important observation in this regard was noted by Lt. Comdr. James B. Black, who examined many patients with acute rheumatic fever at the onset of their illness. When questioned, patients frequently stated that they had no sore throat, but examination often revealed unmistakable evidence of pharyngitis.[10]

Eleven patients were not questioned concerning preceding infection.

Comment: It has been noted for many years by various observers that a close relationship exists between rheumatic fever and a preexisting

TABLE 8.—*Incidence and Rates per Thousand of Various Diseases in the Navy and Marine Corps*

Diagnosis	Incidence					
	1940	1941	1942	1943	1944	1945
Catarrhal fever	27,312	34,050	103,260	281,826	246,037	286,408
Rate per 1,000	134.80	97.59	123.73	133.67	73.45	77.96
Scarlet fever	25	419	1,348	14,041	16,954	27,117
Rate per 1,000	0.12	1.20	1.62	6.66	5.06	7.38
Tonsillitis, acute	4,286	7,160	18,597	55,165	72,719	72,047
Rate per 1,000	20.96	20.52	22.28	26.16	21.71	19.61
Pharyngitis, acute	619	1,229	6,362	26,078	36,744	46,722
Rate per 1,000	3.06	3.52	7.62	12.37	10.97	12.72
Rheumatic fever	140	489	868	5,808	7,668	6,461
Rate per 1,000	0.73	1.40	1.04	2.75	2.29	1.76
Average strength	202,614	348,926	834,639	2,108,379	3,349,798	3,673,855

infection of the upper respiratory tract.[11] The exact nature of this relationship still is not known, and there are those who believe that streptococci play no part in the pathogenesis of rheumatic fever. Pos-

10. Black, J. B.: Personal communication to the author.

11. Coburn, A. F.: Epidemiology of Streptococcus Hemolyticus Infections at Naval Training Stations, U. S. Nav. M. Bull. **41**:1012 (July) 1943. Wheeler, S. M., and Jones, T. D.: Factors in the Control of the Spread of Acute Respiratory Infections with Reference to Streptococcal Illness and Acute Rheumatic Fever, Am. J. M. Sc. **209**:58 (Jan.) 1945. Packard, F. A.: Philadelphia M. J., April 21 and April 28, 1900. Thomson, St.C.: Rheumatic Fever in Relation to the Throat, Practitioner **66**:35, 1901. Kalbak, K.: Undersøgeleser over O-streptolysin og. forekomsten af O-antistreptolysin I serum, Copenhagen, Ejnar Munksgaards forlag, 1942 (English summary). Bruun, E.: Experimental Investigations in Serum Allergy with Reference to the Etiology of Rheumatic Joint Diseases, ibid., 1940. Paul, J. R.: The Epidemiology of Rheumatic Fever and Some of Its Public Health Aspects, ed. 2, New York, Metropolitan Life Insurance Company, 1943.

sibly the truth lies somewhere between these two views, and a combination of a peculiarly susceptible host plus a hemolytic streptococcus infection is necessary in most cases to produce the disease known as rheumatic fever. The Navy's experience lends support to this hypothesis, but since the etiology and pathogenesis of rheumatic fever are still mysteries, there are few facts to recommend one viewpoint above another.

Twenty-four and five-tenths per cent of the patients had rheumatic fever previously, as compared with an estimated 5 to 20 per thousand in the Navy as a whole who had the disease prior to enlistment.[6] Eighty-nine per cent of this group had either an infection of the upper respiratory tract or scarlet fever preceding their rheumatic fever. Only 10 per cent gave no history of a preceding infection of the upper respiratory tract.

9. *Environment of Patients at the Time of Onset of Rheumatic Fever.*—A detailed description of the environment of each person at the time of onset of his illness would be time consuming and confusing. Since the highest incidence of rheumatic fever occurred in boot camps and training schools, it will be most profitable to examine these environments in detail. A word about ships will serve to illustrate a point discussed later. Sleeping and mess compartments on ships were generally crowded, but ventilation was usually excellent. Hours of duty were long and at times strenuous. It is always damp at sea, and frequently men stood long watches in wet clothing, exposed to the elements at their worst. Yet the number who acquired rheumatic fever at sea is small when compared to the total. Another point worth noting is that streptococcic infections are uncommon when a ship has been at sea for more than a few days.

The methods of housing, feeding, and training naval recruits have been described by others,[12] but some of their observations bear repetition because of their importance in the epidemiology of rheumatic fever. Recruits were formed into companies of from 120 to 130, and occasionally the companies numbered 140. New companies were inducted every few days, and their training programs were staggered. They were trained as separate units, but there was ample opportunity for mixing of the companies. In this manner a continuous stream of susceptible persons was introduced into an infected environment. There is much experimental evidence that if an infectious disease is set going in a community and recruits susceptible to the disease are continually introduced into that community, then the disease will persist

12. Schwentker, F. F.; Hodes, H. L.; Kingland, L. C.; Chenoweth, B. M., and Peck, J. L.: Streptococcal Infection in a Naval Training Station, Am. J. Pub. Health **33**:1455 (Dec.) 1943. Coburn, A. F.: The Control of Streptococcus Hemolyticus, Mil. Surgeon **96**:17 (Jan.) 1946.

indefinitely. Greenwood and Topely studied communities of mice for more than ten years, and they did not find any important exception to the rule that an infected herd receiving unselected healthy immigrants will never clear itself of the infectious disease.[13]

During the early months of the war the period of training was from ten to twelve weeks, but later, as the manpower shortage became more acute, the time was shortened to six weeks. The men were housed in two deck barracks, one company to each deck. They slept in double-decked bunks and sometimes triple-decked bunks. The space between the bunks was about 3 feet (91.4 cm.) and less if more than 130 men were housed in a barracks. Mess took place in large halls with galley and scullery facilities for many companies. Recreational facilities, such as the movies and ship's service, were used by everyone at the training center. Swimming pools were used by a large number of different companies.

Sick call was held three times a day at dispensaries, each serving a number of different companies. The sick calls were large and crowded. Patients requiring hospitalization were admitted to dispensaries or naval hospitals located at the training centers. Because of the shortage of beds in the hospital during the epidemic of hemolytic strepococcus infections and because of other reasons, isolation of patients was not carried out. Frequently, men were ill and would not report to "sick call" for several days because they did not want to miss some phase of their training or a liberty or "boot" leave. Often when hospitalized they were sent back to duty before they were completely well, sometimes knowingly by the medical officer and other times innocently. The acute need for beds and the constant pressure and pleadings of patients to get out of the hospital occasionally broke down the firmest resistance of the medical officers. If a man missed too much of his training because of illness, he was not sent back to his old company but to a new one. Frequently the men who had complications from a hemolytic streptococcus infection were sent to new companies.

The decks of the barracks were swept dry twice daily and then swabbed. The wards of the hospital likewise were swept dry, and at least once a week they were buffed with an electric buffer. Frequently a visible cloud of dust rose from the buffer or sweeper. There was no opportunity to leave barracks empty or to clean them thoroughly after a company had completed training. The speeded up training program required every available barracks as soon as it was emptied. Bedding was issued newly to each incoming company, but there was no opportunity for airing or washing bedding during the winter months.

13. Greenwood, M.: The Preventive Aspects of Medicine, Lancet **1**:201 (Jan. 27) 1934.

One central heating unit served each barracks, but seldom did it heat the entire building. As a result the barracks were kept closed as tightly as possible during the winter months, and although adequate ventilation for comfort usually was maintained, conditions were poor from the standpoint of epidemiologic control. Often the opposite state of affairs was true on a ship. During cold weather, men gathered indoors in crowds. Seven hundred and seven (93.4 per cent) of the patients comprising the study group were living in crowded conditions at the onset of their illness. Crowding is not easy to define, but by any standard of adequate housing navy barracks are crowded when filled to capacity.

The great navy recruit training centers were located at Sampson, N. Y., Great Lakes, Ill., Bainbridge, Md., and Farragut, Ida. The weather in these areas is characterized by hot summers and cold winters, with snow and rain in abundance. Foul weather, or macroclimate as it is called by Paul,[14] forced the men indoors for their classes and recreation. In this manner a bad micro-climate was created, that is, one which favored the spread of contagious disease. Dampness is difficult to measure, and the role it plays in the pathogenesis of rheumatic fever is not understood; however, 640 patients (85 per cent) considered their environment to be damp when they became ill.

At one time the Navy was faced with a desperate situation wherein epidemics of hemolytic streptococcus infection were a grave menace to the training program. Because of the seriousness of the problem, prophylaxis with sulfonamide compounds was instituted.[15] The incidence of hemolytic streptococcus infections was reduced dramatically, and at the same time the rate of rheumatic fever fell; these reductions, however, were only temporary (table 8). Later, certain strains of hemolytic streptococci acquired resistance to the sulfonamide compounds and the incidence of infection by these organisms returned to epidemic proportions.[16] Similar experiences were observed in other naval and army establishments.

In the Navy, as in civilian life, patients with scarlet fever are isolated or quarantined when facilities for such are available. On the other hand, only in rare instances were patients with hemolytic strepto-

14. Paul, J. R.: Macro-Climate and Micro-Climate in Rheumatic Fever, Tr. Am. Clin. & Climatol. A. (1941) **57**:172, 1942.

15. The Prevention of Respiratory Tract Bacterial Infections by Sulfadiazine Prophylaxis in the United States Navy, United States Navy Department, Bureau of Medicine and Surgery, 1944.

16. Sulfadiazine Resistant Strains of Beta Hemolytic Streptococci, J. A. M. A. **129**:921 (Dec. 1) 1945. Damrosch, D. S.: Chemoprophylaxis and Sulfonamide Resistant Streptococci, ibid. J. A. M. A. **130**:124 (Jan. 19) 1946.

coccus infections isolated. This same questionable practice is carried on in civilian life.

It is not within the scope of this study to describe the work of the Navy Epidemiologic Units in studying and attempting to prevent the conditions which were of epidemiologic importance in naval training centers. It also should be pointed out that it is not possible to describe individual variations in the epidemiologic pattern which existed in different training centers; only the general pattern has been discussed.

COMMENT

This study does not pretend to give a picture of the epidemiology of rheumatic fever in the Navy as a whole. What has been said applies only to the 757 patients under consideration. It is evident that when this group of young men, susceptible to rheumatic fever, were introduced into a crowded community in which hemolytic streptococcus infection and rheumatic fever were epidemic they acquired rheumatic fever. It is impossible to know at present all the factors in the individual person or in the community which are of significance in the epidemiology of the disease. However, in relation to this study, it was found that of importance were the factors of intermittent introduction of susceptible recruits into an infected environment, crowding, previous rheumatic fever, preceding infection of the upper respiratory tract, relatively young "Navy age," possibly the strenuous duties of boot training and the location of the boot camps in areas in which the civilian death rate for rheumatic fever was high.

SUMMARY AND CONCLUSIONS

1. A group of 757 enlisted male personnel with rheumatic fever in the United States Navy and Marine Corps were included in an epidemiologic study.

2. The rate of rheumatic fever for the United States Army and Navy increased sharply during both World War I and World War II. Rates in the Navy were as follows: 1940, 0.73; 1931, 1.40; 1942, 2.75; 1943, 2.29, and 1945, 0.52. In the Army there were the following rates: 1940, 0.36; 1941, 0.83; 1942, 0.51; 1943, 1.08; 1944, 0.72, and 1945, 0.52.

3. That 24.5 per cent of the study group had had previously recognized rheumatic fever before enlisting in the Navy or Marine Corps is highly significant. This knowledge suggests that these persons were highly susceptible to rheumatic fever.

4. A majority of patients came from urban homes. The areas which produced the largest numbers and percentages of patients with

rheumatic fever prior to enlistment were the North Central states, the New England states, the South Atlantic states, and the Middle Atlantic states.

5. The age at the time of the first attack of rheumatic fever (17 to 19 inclusive) in the majority of patients was considerably higher than the age at onset for the majority in the civilian population (7 to 10 inclusive).

6. The age range of the patients was from 17 to 43 inclusive. Sixty-one per cent were of the ages 17, 18 and 19. Rheumatic fever occurred more often in patients at the age of 18 than in patients of any other age (279, or 36.9 per cent).

7. The large proportion of men who had a recrudescence of rheumatic fever after enlistment (24.5 per cent) suggests that these persons were especially susceptible to the disease and that factors were present in the new environment which favored reactivation of the rheumatic process.

8. The number of attacks per person after enlistment was the same for those with as for those without previous rheumatic fever.

9. The highest rates of rheumatic fever in the Navy were present in the training centers. The rate for personnel at sea or in foreign shore stations was low. Naval training centers were located in areas in which the death rate for rheumatic fever among civilians was high.

10. In general, the duties of the study group were not different from those of enlisted personnel in the Navy or Marine Corps who did not acquire rheumatic fever.

11. Seventy-seven and two-fifths per cent of the patients acquired their present illness during the first year of their "Navy life." Seventy-nine and three-fifths per cent of these acquired rheumatic fever during their first six months in the Navy.

12. With environmental factors favorable for the development of an epidemic of rheumatic fever and the introduction of susceptible hosts into this environment, rheumatic fever can occur at any season.

13. Seventy-four and two-fifths per cent of the patients had an infection of the upper respiratory tract which preceded the onset of rheumatic fever by an interval of from two to sixty days, with an average of about eighteen days. Laboratory proof that these infections were caused by hemolytic streptococci is lacking. However, the infections occurred in the presence of epidemic hemolytic streptococcus infections, and the clinical characteristics of the two were indistinguishable. Fifteen and three fifths per cent of the patients had scarlet fever preceding rheumatic fever. Ten per cent had no infection of the upper respiratory tract prior to the rheumatic fever.

14. This study adds further evidence that hemolytic streptococcus infection plays a part in the pathogenesis of rheumatic fever.

15. The staggered introduction of fresh recruits and the high degree of crowding of both infected and susceptible persons in semiclosed spaces with inadequate ventilation from an epidemiologic standpoint, plus a constant secondary reservoir of infective material in bedding and floor dust, favored the development of epidemics of hemolytic streptococcus infections followed by an epidemic of rheumatic fever.

Captain F. R. Lang, of the Medical Corps of the United States Navy, Chief of the Medical Statistics Division, Bureau of Medicine and Surgery, Navy Department, and Eugene L. Hamilton, Director, Medical Statistics Division, Office of the Surgeon General, War Department, supplied valuable data used in making tables 1, 2, 3, 4 and 7.

LOW SERUM POTASSIUM LEVEL DURING RECOVERY FROM DIABETIC COMA

With Special Reference to Its Cardiovascular Manifestations

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DURING the treatment of a patient with severe diabetic coma, we had the opportunity to observe an alarming clinical syndrome, which was probably due to a condition of extreme potassium depletion.

REPORT OF A CASE

Mrs. B., aged 56 and mother of five children, was admitted to the hospital on July 27, 1946, at 8 p. m. in severe diabetic coma. The past history was noncontributory but for the fact that she had been extremely obese as a young girl and that she was known to have had diabetes for twelve years. She took 20 units of regular insulin daily but was always negligent about her diet. No members of her family were known to have suffered from any special diseases. There was no history of periodic muscular paralysis in the family.

On July 23 the patient noticed a furuncle on her nose. She was tired and thirsty and had a complete lack of appetite. She drank a lot, and about every fifteen minutes she had to void urine. On July 26 she began to vomit. On July 27 she awoke with intense pain in the upper abdominal area. During the rest of the day she became increasingly drowsy. She had omitted her insulin since July 23.

Physical Examination.—Examination on admission of the patient to the hospital revealed an emaciated, dehydrated woman in deep coma with acidotic respiration. There was a strong acetone odor of the breath. The eyeballs were extremely soft. The pulse was regular with a frequency of 98 per minute, and the respiratory rate was 32. The rectal temperature was 36 C. (96.8 F.) and the blood pressure 160 systolic and 80 diastolic. There was a furuncle on the nose. No other significant abnormalities were found on internal examination. Neurologic examination revealed narrow, sluggish pupils and the absence of tendon reflexes.

Laboratory Examination.—Urinalysis gave strongly positive reactions for albumin, glucose, acetone and diacetic acid. The sediment contained erythrocytes and short granular casts. Chemical examination of the blood on admission gave these values: glucose, 486 mg.; plasma bicarbonate, 6 volumes per cent (2.7 milliequivalents); urea, 65 mg.; serum chloride, 376 mg. (103 milliequivalents); sodium, 340 mg. (148 milliequivalents), and potassium, 20.8 mg. (5.3 milliequivalents) per hundred cubic centimeters.

From the Second Medical Service of the Wilhelmina Gasthuis.

Course in the Hospital.—In view of the severe acidosis, an intensive treatment was started. The patient received at once 200 units of regular insulin (of which 100 units were administered intravenously) and 60 units subcutaneously at hourly intervals. During the first fifteen hours, 2,000 cc. of isotonic solution of sodium chloride, 1,000 cc. of a 5 per cent solution of sodium bicarbonate and later 2,000 cc. of a 10 per cent solution of dextrose were administered by intravenous drip. After three hours of treatment, chemical examination of the blood showed no improvement; at this point another 200 units of insulin was administered intravenously and 100 units subcutaneously. Gastric lavage was performed, and black coffee-ground material was removed. From then on the blood sugar level started to fall and the plasma bicarbonate level began to rise. As further measures against signs of impending shock, 500 cc. of whole blood and 250 cc. of plasma were given. To combat the infection, the patient received 30,000 units of penicillin every three hours. The next day at 10 a. m. the condition seemed greatly improved. She had regained consciousness and seemed fairly comfortable. At this time the blood sugar level was 140 mg. per hundred cubic centimeters and the plasma bicarbonate 60 volumes per cent. She had received a total of 1,500 units of regular insulin.

Fifteen hours after initiation of treatment, the patient complained of shortness of breath. At 1 p. m. she was covered with clammy perspiration. The clinical picture for a moment suggested hypoglycemia. Blood was taken for analysis and 50 Gm. of dextrose in 20 per cent solution immediately administered by vein. Thereupon the perspiration ceased, but the general condition deteriorated quickly. At this time the blood sugar value before the administration of dextrose became known. It was 117 mg. per hundred cubic centimeters, and it was obvious that the change in the clinical picture could not be due to hypoglycemia. The situation in the meantime had become alarming. In particular, the following phenomena were observed:

1. The patient complained of shortness of breath. She gasped for breath, and it was noticed that the respiratory movements were performed only with the upper part of the chest. This was carried out by active participation of the auxiliary respiratory muscles; the lower part of the chest remained immobile. At each inspiration the mouth opened and the tongue protruded in a manner seen in succumbing patients. For this reason, we can best describe the respiratory pattern as "agonal breathing."[1]

2. The patient showed a generalized muscular weakness. The muscles of the extremities, especially the arms, were distinctly flaccid and hypotonic. The tendon reflexes were still absent.

3. The pulse was irregular. On auscultation we got the impression that this was due to premature beats.

4. The cardiac dulness, which had been normal on the patient's admission to the hospital, was now definitely increased, especially to the left. The apex beat was diffuse and heaving.

5. Over the whole cardiac area a harsh systolic murmur was heard, which had not been there before.

6. The blood pressure, which had fallen during the night to 115 systolic and 65 diastolic, now had risen to 155 systolic and 60 diastolic. The increased pulse pressure manifested itself in a pronounced Corrigan's pulse.

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1. Dr. R. F. Loeb, of Presbyterian Hospital, New York, calls this type of respiration "fish mouth breathing." This seems to us an appropriate designation.

7. The neck veins were engorged to about 7 cm. above the level of the angulus Ludovici. There were no signs of pulmonary edema.

What could be the cause of this alarming syndrome in a patient who only a few hours before appeared to be recovering satisfactorily from her coma? We knew from previous experience that overdosage of insulin was sometimes accompanied with a fall in the serum potassium level. We further knew from the literature on familial periodic paralysis and other conditions accompanied with a low serum potassium level that such a fall can occur together with a typical clinical syndrome. We had been struck, in reading some descriptions of the attack of periodic paralysis, by the combination of muscular weakness with respiratory distress and irregularities of the pulse. This led us to suspect that the alarming syndrome in this patient who had been treated with unusually large quantities of insulin might be due to a low serum potassium level. Accordingly, we took blood for a potassium determination, and without waiting for the result we administered twice, at short intervals, 2 Gm. of potassium chloride in solution by mouth. The effect was striking. Within half an hour the patient gave a completely different impression. She became interested in her surroundings and asked for food. Her respiration became normal. Muscular weakness, irregularity of the pulse and cardiac murmur had disappeared. The blood pressure one-half hour after the first dose of potassium chloride was 135 systolic and 80 diastolic. The venous pressure was normal. Further recovery was uneventful. A few hours later the report came back from the laboratory that the serum potassium, which had been 20.8 mg. per hundred cubic centimeters on admission, had fallen at the critical moment to 7.4 and 6.3 mg. (duplicate estimations, averaging 1.8 milliequivalents). After the administration of potassium, the level was not determined until the next day, when it had risen to 13.5 mg. per hundred cubic centimeters. A few days later, after the patient had completely recovered, we found normal values of 24 to 25 mg.

COMMENT

About one month after this observation, we received *The Journal of the American Medical Association* of Aug. 10, 1946, in which Holler [2] described a case which in many respects was similar to ours. His patient was a diabetic girl of 18 years who was admitted to the hospital in coma. She also received intensive treatment with insulin and a solution of dextrose and sodium chloride. Of the latter, she got 17 liters by vein during the first twenty-four hours. After the first twelve hours of treatment, she became restless and dyspneic. The respiratory distress was due to a paralysis of the diaphragm and the lower intercostal muscles; it became so severe after twenty-four hours that she had to be placed in a Drinker respirator. Several attempts to take her out of the respirator resulted in a distressing recurrence of the dyspnea. After twenty-four hours, about twelve hours after the first appearance of the alarming signs, the possibility of a potassium depletion was considered. The serum potassium was at this time 9.8 mg. per hundred cubic centimeters. Potassium chloride was administered by vein and

2. Holler, J. W.: Potassium Deficiency Occurring During the Treatment of Diabetic Acidosis, J. A. M. A. **131**:1186 (Aug. 10) 1946.

potassium citrate by mouth, with striking result. In addition to the respiratory paralysis, the author reported the following abnormalities of the electrocardiogram: Before administration of potassium, a severe tachycardia was found. The second and the third lead showed negative P waves, QRS time was prolonged and QRS in lead III slurred; in all three classic leads the S-T segments were depressed and the T waves were low. After the administration of potassium, the cardiac rate slowed down, and a new electrocardiogram showed that the abnormalities had almost completely disappeared.

On analysis of our case, the following problems have to be considered: 1. What was the relation between the low serum potassium level and the clinical syndrome in this patient? 2. Which factors were responsible for the fall in the serum potassium level?

In order to explain the relation between the low serum potassium content and the clinical picture, we can best compare the situation with that occurring during an acute attack of familial periodic paralysis. This hereditary disease is characterized by paroxysms of muscular paralysis, during which severe dyspnea has been frequently noted. The respiratory distress during the attack is due to a paralysis of the diaphragm and the intercostal muscles. It is remarkable that the accessory respiratory muscles and the muscles which are innervated by the cranial nerves are almost never involved in the paralysis. Irregular action of the heart, cardiac dilatation and systolic murmurs during the attacks have been described.[3] Biemond and Polak Daniels [4] described "remarkable throbbing of the peripheral arteries" in their case during an attack. Changes in the electrocardiogram during the attack have been studied by Stewart and others.[5] The serum potassium content has always been found significantly low during the attack whenever it has been determined.[6] Administration of potassium salts causes a rapid disappearance of the paralysis together with the other signs.

3. Talbot, J. H.: Period Paralysis, Medicine **20**:85, 1941.

4. (*a*) Biemond, A., and Polak Daniels, A.: Over het verband tusschen paroxysmale verlamming en progressive spierdystrophie, Nederl. tijdschr. v. geneesk. **78**:1071, 1934; (*b*) Familial Periodic Paralysis and Its Transition into Spinal Muscular Atrophy, Brain **57**:91, 1934.

5. Stewart, H. J.; Smith, J. J., and Milhorat, A. T.: Electrocardiographic and Serum Potassium Changes in Familial Period Paralysis, Am. J. M. Sc. **199**:709, 1940.

6. (*a*) Aitken, R. S.; Allott, E. N.; Castleden, L. I. M., and Walker, M.: Observations on a Case of Familial Periodic Paralysis, Clin. Sc. **3**:47, 1937. (*b*) Allott, E. N., and McArdle, B.: Further Observations on Familial Periodic Paralysis, ibid. **3**:229, 1938. (*c*) Pudenz, R. H.; McIntosh, J. F., and McEachern, D.: The Role of Potassium in Familial Periodic Paralyis, J. A. M. A. **111**: 2253 (Dec. 17) 1938. (*d*) Talbot.[3] (*e*) Biemond and Polak Daniels.[4b]

In other conditions of potassium depletion, muscular paralysis together with shortness of breath, cardiac arrhythmia and changes in the electrocardiogram have also been described. Brown, Currens and Marchand [7] observed similar symptoms in 2 cases of chronic nephritis with low serum potassium. Administration of potassium resulted in rapid relief of the symptoms. Thorn and his co-workers [8] witnessed two attacks of transient paralysis associated with an abnormal lowering of the serum potassium level in a patient with Addison's disease who had been given large quantities of desoxycorticosterone in addition to intravenously administered sodium chloride and dextrose. In consideration of these facts, it seems justified to suppose that various conditions in which a considerable drop in serum potassium takes place may also give rise to a disturbance of muscle metabolism of such a degree that it may result in paralysis of the extremities, in respiratory paralysis and in a disturbance in the function of the heart muscle. The experiments of Kuhlmann [9] and of Ferrebee and others [10] support this hypothesis. After administration of large doses of desoxycorticosterone in dogs, these authors observed a drop in serum potassium which was sometimes accompanied with muscular paralysis.

It is not known at present if there exists a critical level below which the serum potassium must fall before the syndrome of generalized muscular paralysis makes its appearance. Aitken, Allott, Castleden and Walker [6a] reported that an attack occurred in their patient with familial periodic paralysis as soon as the serum potassium dropped below 12 Gm. per hundred cubic centimeters. Allott and McArdle,[6b] however, found a less rigid relationship between the serum potassium level and the occurrence of the attacks. In view of further experiences with other patients, we are inclined to doubt that there is such a thing as a critical serum potassium level, but it is certain that the content must be significantly lowered before clinical manifestations can be expected.

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7. Brown, M. R.; Currens, J. H., and Marchand, J. F.: Muscular Paralysis and Electrocardiographic Abnormalities Resulting from Potassium Loss in Chronic Nephritis, J. A. M. A. **124**:545 (Feb. 26) 1944.

8. Thorn, G. W.: Desoxycorticosterone, J. Mt. Sinai Hosp. **8**:1177, 1942. Thorn, G. W.; Dorrance, S. S. and Day, E.: Addison's Disease: Evaluation of Synthetic Desoxycorticosterone Acetate Therapy in One Hundred and Fifty-Eight Patients, Ann. Int. Med. **16**:1053, 1942.

9. Kuhlmann, D.; Ragan, C.; Ferrebee, J. W.; Atchley, D. W., and Loeb, R. F.: Toxic Effects of Desoxycorticosterone in Dogs, Science **90**:496, 1939.

10. Ferrebee, J. W.; Parker, D.; Carnes, W. H.; Gerity, M. K.; Atchley, D. W., and Loeb, R. F.: Replacement of Potassium by Sodium in Muscles of Normal Dogs Receiving Desoxycorticosteroneacetate, J. Clin. Investigation **20**:445, 1941; Certain Effects of Desoxycorticosterone: Development of Diabetes Insipidus and Replacement of Muscular Potassium by Sodium in Normal Dogs, Am. J. Physiol. **135**:230, 1941.

Different factors cooperated to cause the drop in serum potassium in our patient. For an understanding of the situation, it is best to distinguish between the potassium balance which existed at the time of admission and the influence thereon of the ensuing therapy. Before and during the first hours of hospitalization, the patient had not taken any food; she had ingested only large quantities of water. The classic researches of Atchley, Loeb, Dickinson, Benedict and Driscoll [11] and those of Wiley and Wiley and Waller [12] have shown that a considerable loss of potassium through the urine occurs during diabetic acidosis. This loss is probably due to a combination of the copious diuresis and the increased glycosuria (case 2 in the study by Atchley and others), acidosis (case 1 in the same study) and dehydration.[12b]

There may be other causes for this loss of potassium. It is well known that in untreated diabetes part of the body protein from the cells liberates nitrogen as well as large quantities of potassium and phosphorus, and these substances are consequently excreted in the urine. The vomiting and gastric lavage may also have contributed to the loss of potassium. Gastric juice contains not inconsiderable amounts of potassium—according to Austin and Gammon [13] two and one-half times as much as blood serum. We have frequently found the potassium content of vomitus to be between 40 and 50 mg. per hundred cubic centimeters.[14]

Thus, it may be assumed that at the moment when treatment was started our patient had ingested little potassium and had lost a considerable quantity. This potassium depletion of the body must have resulted in a diminution of the intracellular potassium stores. Probably there was also a diminution of the volume in the extracellular fluid. However, although the potassium balance was already negative when the patient came in, the potassium level of the serum had remained normal up to this point. It only began to fall when treatment was instituted. This treatment consisted in administration of large amounts of insulin, water, dextrose, sodium chloride and sodium bicarbonate

11. Atchley, D. W.; Loeb, R. F.; Dickinson, W. R.; Benedict, E. M., and Driscoll, M. E.: On Diabetic Acidois: A Study of Electrolyte Balances Following the Withdrawal and Re-Establishment of Insulin Therapy, J. Clin. Investigation **12**:297, 1933.

12. (*a*) Wiley, F. H.; Wiley, L. L., and Waller, D. S.: The Effect of the Ingestion of Sodium, Potassium, and Ammonium Chloride and of Sodium Bicarbonate on the Metabolism of Inorganic Salts and Water, J. Biol. Chem. **101**:73, 1933. (*b*) Wiley, F. H., and Wiley, L. L.: The Inorganic Salt Balance During Dehydration and Recovery, ibid. **101**:83, 1933.

13. Austin, J. H., and Gammon, G. D.: Gastric Secretion After Histamine: Sodium and Potassium Content and Pepsin Estimation, J. Clin. Investigation **10**:287, 1931.

14. Frenkel, M.; Groen, J., and Willebrands, A. F.: Unpublished observations.

(still no potassium). How is the drop in the serum potassium which occurred with these measures to be explained?

As early as 1923 and 1924 Harrop and Benedict [15] and Briggs, Koechig, Doisy and Weber [16] described a drop in serum potassium after injection of large doses of insulin in persons with diabetes, in normal persons and in experimental animals. Their observations were confirmed by different authors, especially by Kerr [17] in pancreatectomized dogs. Later a low serum potassium level was found by Harris, Blalock and Horwitz [18] in patients with psychosis during induced insulin shock. In Holland, a low serum potassium content during induced hypoglycemic shock was described by Drooglever Fortuyn.[19] Recently, we determined the serum potassium in 2 diabetic patients who were admitted in hypoglycemic coma.[14] The levels were 13 and 14 mg. per hundred cubic centimeters respectively.

Most investigators ascribe the drop in serum potassium to the fact that insulin causes the potassium to shift from the extracellular fluid into the cells.[20] Some believe that potassium as well as phosphate is used up in one of the first stages of storage or combustion of carbohydrate by the action of insulin. Another possibility is that potassium, together with water, is taken up by the hepatic cells during the synthesis of glycogen (Fenn [21]). A third hypothesis, which seems likely, is that during the rapid correction of the metabolic disturbance which takes place during treatment of diabetes proteins, which had been destroyed during the coma, are being rebuilt. This synthesis requires the fixation of water and potassium in the cells. Which of these hypothetic mechanisms actually plays the most important role is undecided. The only thing that is known for certain is that the potassium which disappears from the extracellular fluid after the administration of insulin is not excreted in the urine. Our own experiences with other cases of diabetic

15. Harrop, G. A., and Benedict, E. M.: The Participation of Inorganic Substances in Carbohydrate Metabolism, J. Biol. Chem. **59**:683, 1924.

16. Briggs, A. P.; Koechig, I.; Doisy, E. A., and Weber, C. J.: Some Changes in the Composition of the Blood Due to the Injection of Insulin, J. Biol. Chem. **58**:721, 1923.

17. Kerr, S. E.: The Effect of Insulin and Pancreatectomy on the Distribution of Phosphorus and Potassium of the Blood, J. Biol. Chem. **128**:35, 1938.

18. Harris, M. M.; Blalock, J. R., and Horwitz, W. A.: Metabolic Studies During Insulin Hypoglycemia Therapy of Psychosis, Arch. Neurol. & Psychiat. **40**:116, (July) 1938.

19. Drooglever Fortuyn, J.: Hypoglycemia and the Autonomic Nervous System, J. Nerv. & Ment. Dis. **93**:1, 1941.

20. Guest, G. M.: Organic Phosphates and Mineral Metabolism in Diabetic Acidosis, Am. J. Dis. Child. **64**:401 (Sept.) 1942.

21. Fenn, W. O.: The Deposition of Potassium and Phosphate with Glycogen in Rat Livers, J. Biol. Chem. **128**:297, 1939; The Role of Potassium in Physiological Processes, Physiol. Rev. **20**:337, 1940.

coma confirm the former observations that as soon as insulin is given excretion of potassium in the urine decreases.

The migration of potassium from the extracellular fluid into the cells does not take place with low blood sugar levels only. It is a regular part of a physiologic mechanism, inherent in the action of insulin. In other patients with diabetic coma [14] we have maintained high blood sugar levels throughout the treatment by administering large quantities of dextrose together with the insulin. Nevertheless, these patients showed a similar drop in serum potassium.

Most patients with diabetic coma do not show any clinical manifestations associated with this potassium shift. If the patient is given food early during the treatment, the shift is masked by the concomitant intake of potassium and there will be no drop in serum potassium. In other cases, the serum potassium may drop, but the shift of potassium from extracellular to intracellular space is not decided enough to cause clinical manifestations, and therefore it is not noted. Only in cases of severe diabetic coma, as in Holler's and in our case, in which the potassium stores of the body were already depleted on entry, no food (and hence no potassium) was given and unusually large amounts of insulin were administered, may the level of potassium drop so low. The potassium shift may then produce the clinical syndrome of generalized muscular insufficiency. It does not seem improbable, however, that this syndrome has been overlooked in a number of cases, and it may have been the cause of the "unexplained" death of patients with diabetic coma in spite of correction of the shock and the chemical abnormality of the blood.[22] Of these deaths, Wilder,[23] stated: "Usually they are sudden deaths, suggesting pulmonary embolism and shock or acute dilatation of the heart, but at necropsy no emboli can be found and the heart is not greatly dilated. In some such cases the heart stops before the respiration, although in other cases respiratory failure occurs first." Joslin and others [24] have also commented on the unexplained death of some patients with diabetic coma in whom a "gasping respiration" develops. The modern tendency to bring the patient with diabetic acidosis out of his coma within the shortest possible time may actually contribute to the occurrence of this dangerous situation.

It is more difficult to evaluate the effect of the other therapeutic measures on the development of the "potassium depletion syndrome." Our patient, as well as Holler's, received large quantities of fluid to com-

22. Butler, A. M., in discussion on Diabetes Mellitus with Acidosis, Cabot Case 30451, New England J. Med. **231**:657, 1944.

23. Wilder, R. M.: Clinical Diabetes Mellitus and Hyperinsulinism, Philadelphia, W. B. Saunders Company, 1941, P. 180.

24. Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: Treatment of Diabetes Mellitus, ed. 8, Philadelphia, Lea & Febiger, 1946.

bat dehydration. In our case 5,000 cc. was administered during the first twelve hours; Holler's patient received 17,000 cc. in twenty-four hours, of which 15,000 cc. was eliminated by the kidneys during the same time. Part of this fluid was retained in the rehydrated body cells together with potassium. Another part of the retained water diluted the extracellular fluid. It seems probable that this rehydration with a fluid not containing any potassium contributed to the fall in serum potassium concentration.

The administration of large amounts of dextrose may cause a fall in the serum potassium level in normal subjects. Aitken and others [6a] found a serum potassium level of 16 mg. per hundred cubic centimeters in normal subjects after ingestion of 250 Gm. of dextrose. The underlying mechanism is probably the same as that occurring after administration of insulin. An extremely low serum potassium level, as was found in our case, has never been obtained, however, by administration of dextrose alone. We do not believe that 18 Gm. of sodium chloride, which our patient received in isotonic solution, can have played a major role. The influence of the administration of large quantities of sodium bicarbonate (50 Gm. in our case) on potassium metabolism is not completely elucidated. Darrow [25] observed a loss of muscular potassium and sometimes a decrease in serum potassium after intraperitoneal injection of sodium bicarbonate in rats. We [14] observed a drop of the serum potassium level in 2 patients after administration of 1,000 cc. of a 5 per cent solution of sodium bicarbonate by vein. The mechanism of this drop, however, is entirely different from what we observed in the case under discussion, because it was found that the infusion of sodium bicarbonate gave rise to an increased excretion of potassium in the urine.

Finally, we wish to stress that in the syndrome of potassium depletion combined with a potassium shift into the cells, as we have seen it in our patient, three different groups of phenomena should be distinguished. The first group consists in muscular paralysis and dyspnea. This may be called the syndrome of generalized muscular insufficiency. In the second place, our patient showed a number of circulatory phenomena: (1) an increased pulse pressure; (2) a collapsing pulse; (3) an increase of the cardiac dulness; (4) a systolic murmur, and (5) a high venous pressure. This is the cardiovascular syndrome known as "high output failure" or "arteriovenous shunt syndrome." We feel that it forms part of the clinical syndrome associated with this particular disturbance of potassium metabolism. We had the opportunity since to observe the same syndrome several times in instances of insulin overdosage. The large pulse pressure as well as the high venous pressure has been

25. Darrow, D.: Changes in Muscle Composition in Alkalosis, J. Clin Investigation **25**:324, 1946.

described by Kugelmann [26] and by Lauter and Baumann [27] in hypoglycemic shock. We consider it more likely that these phenomena are due to the concomitant potassium changes rather than to a low blood sugar level. The fact that we observed them in a patient who was not hypoglycemic and that they did not disappear after administration of dextrose but did so after administration of potassium supports this assumption. In the third place, the regular association of certain changes in the electrocardiogram with this condition of potassium shift seems of interest. Here again, it is striking that the electrocardiographic changes which have been described after overdosage of insulin are exactly the same as those seen with a low serum potassium level [28] and during the attacks of periodic paralysis.[5] They consist essentially in a depression of the S-T segment and in low voltage of the T waves. We suppose that the electrocardiographic changes observed by Bellet and Dyer [29] in patients who recovered from diabetic coma are probably due to the same mechanism. We suggest that these changes are due not to a low blood sugar level, as has sometimes been assumed, but to a shift of potassium from extracellular to intracellular space inside the heart muscle. Actually, several investigators have observed that the changes in the electrocardiogram after overdosage of insulin may occur with an insignificant drop of the blood sugar level whereas they are sometimes absent when the blood sugar level is extremely low.[27a]

It is too early to decide whether this shift in potassium and the clinical effects thereof are a direct result of the action of insulin. The possibility should also be borne in mind that they are due to an increased secretion of epinephrine or of one of the adrenal cortex hormones taking place as a counter regulation after overdosage of insulin. We also feel that it is unjustified to ascribe the clinical syndrome associated with the potassium shift to the low serum potassium level itself. It seems more probable that changes in the intracellular potassium occurring with this shift are responsible.

SUMMARY

During treatment of a patient in severe diabetic coma with large quantities of insulin, water, dextrose, sodium chloride and sodium bicarbonate, we observed a syndrome of muscular weakness, gasping type of respiration due to paralysis of the lower respiratory tract,

26. Kugelmann, B.: Ueber die Beziehungen zwischen Insulin und Adrenalin im menschlichen Organismus, Klin. Wchnschr. **10**:59, 1938.

27. Lauter, S.; and Baumann, H.: Kreislauf und Atmung im hypoglycaemischen Zustand, Deutsches Arch. f. klin. Med. **163**:161, 1929.

28. (*a*) Scherf, D., and Boyd, L. D.: Clinical Electrocardiography, London, William Heinemann, Ltd., 1945. (*b*) Brown and others.[7] (*c*) Holler.[2]

29. Bellet, S., and Dyer, W. W.: The Electrocardiogram During and After Emergence from Diabetic Coma, Am. Heart J. **13**:72, 1937.

irregular Corrigan's pulse, large pulse pressure, dilatation of the heart, a systolic murmur and high venous pressure. Abnormalities of the electrocardiogram have also been noted in this condition. The syndrome manifested itself after the blood sugar and blood bicarbonate levels had returned to normal. It was found that the serum potassium content, which had been normal on the patient's admission to the hospital, had fallen to 6.9 mg. per hundred cubic centimeters. The conclusion is reached that this drop was most likely caused by a loss of potassium from the body during the period of acidosis, a low potassium intake for several days and a shift of potassium from extracellular to intracellular fluid under the influence of large doses of insulin.

It has been the purpose of this paper to (1) describe how, during a too energetic treatment of diabetic coma, a dangerous condition may occur which is due to potassium depletion, (2) draw attention to a typical clinical syndrome which may be a manifestation of this condition, (3) stress the value of early recognition of this complication, as it can be treated successfully by the administration of potassium, and (4) suggest the possibility that some of the vegetative manifestations of insulin "shock" are due not to hypoglycemia but to a shift of potassium from extracellular to intracellular space.

NOTE: Since this paper was submitted for publication, the following pertinent articles have appeared in the literature: Martin, H. E., and Wertman, M.: Serum Potassium, Magnesium and Calcium Levels in Diabetic Acidosis, J. Clin. Investigation **26**:271, 1947. Nicholson, W. M., and Branning, W. S.: Potassium Deficiency in Diabetic Acidosis, J. A. M. A. **134**:1292 (Aug. 16) 1947.

METABOLIC STUDIES IN DIABETIC ACIDOSIS

I. The Effect of the Early Administration of Dextrose

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DETROIT

IT IS generally agreed that diabetic acidosis develops from excessive production of ketone in the body consequent on diminished glucose oxidation and depletion of liver glycogen. In order to check production of ketone, therapeutic efforts have been directed toward acceleration of glucose oxidation and restoration of liver glycogen. Soskin [1] and Mirsky [2] have found that the maintenance of considerable hyperglycemia through the intravenous injection of large amounts of dextrose accelerated glucose oxidation and glycogenesis in the liver and the disappearance of ketosis. For this reason it had been our custom to begin administration of dextrose early in the treatment of diabetic coma, while hyperglycemia was still present. However, the development of fatal circulatory collapse or cardiac failure during the course of therapy has led us to reevaluate the effects of early administration of large amounts of dextrose on the carbohydrate metabolism, acidosis, water balance and clinical course of diabetic coma.

PROCEDURE

The studies reported in this paper were carried out during the first twenty-four hours of hospitalization on 28 patients admitted in severe

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1. Soskin, S., and Levine, R.: A Relationship Between the Blood Sugar Level and the Rate of Sugar Utilization Affecting the Theory of Diabetes, Am. J. Physiol. **120**:761, 1937.

2. Mirsky, I. A.; Heiman, J. D., and Broh-Kahn, R. H.: The Antiketogenic Action of Glucose in the Absence of Insulin, Am. J. Physiol. **118**:290, 1937.

diabetic acidosis or coma. Complete physical examination was made on admission, and special attention was directed to the cardiovascular status and to the presence of other complications. Frequent observations were made of the mental state, blood pressure and degree of hydration throughout the course of therapy. For the sake of uniformity, the clinical observations were made throughout by us.

Accurate records were kept of all intake. This was limited to water, sodium chloride, dextrose and insulin, supplemented in some cases by crystalline vitamins, alkali, plasma, blood or sodium phosphate. The cases were divided into three groups, according to therapeutic regimen. The first group received no supplementary dextrose until the blood sugar level had fallen within the normal range. (This group is hereafter referred to as the "saline" group.) The second group received dextrose intravenously or orally from the onset of therapy (hereafter called the "dextrose" group). The third group were also started on dextrose early, but in addition they received buffered sodium phosphate solution beginning within three and one-half to nine hours after the onset of therapy (hereafter designated as the "phosphate" group). The discussion of the course of the phosphate group after the first four hours is reserved for another paper.

Samples of heparinized blood were collected immediately after admission of the patients to the hospital and at approximately four hour intervals thereafter. Each specimen was analyzed for (1) inorganic phosphorus by the method of Fiske and Subbarow,[3] (2) glucose by the method of Folin and Wu,[4] (3) chloride by the method of Saifer and Kornblum[5] and (4) carbon dioxide–combining power by the method of Van Slyke and Cullen.[6] Hematocrit readings were done with accurately graduated centrifuge tubes and the specific gravity of the plasma was determined by the falling drop method of Phillips, Van Slyke and others,[7] with copper sulfate standards.

An indwelling catheter was installed, and the bladder was emptied prior to the onset of therapy. All urine thereafter was collected under

3. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375, 1925.

4. Folin, O., and Wu, H.: A Simplified and Improved Method for the Determination of Sugar, J. Biol. Chem. **41**:367, 1920.

5. Saifer, A., and Kornblum, M.: Determination of Chlorides in Biological Fluids by the Use of Adsorption Indications, J. Biol. Chem. **112**:117, 1935.

6. Van Slyke, D. D., and Cullen, G. E.: Studies of Acidosis: I. The Bicarbonate Concentration of the Blood Plasma; Its Significance and Its Determination as a Measure of Acidosis, J. Biol. Chem. **30**:289, 1917.

7. Phillips, R. A.; Van Slyke, D. D.; Dole, V. P.; Emerson, K., Jr.; Hamilton, P. B., and Archibald, R. M.: The Copper Sulfate Method for Measuring Specific Gravities of Whole Blood and Plasma, Bull. U. S. Army M. Dept., 1943, no. 71, p. 66.

toluene in fractional specimens in the intervals between the collection of blood samples. Quantitative urinalyses were made for (1) phosphorus by the method of Fiske and Subbarow,[8] (2) glucose by the method of Benedict,[8] (3) chloride by the Volhard-Arnold method [9] and (4) nitrogen by the method of Koch and McMeekin.[10] Qualitative urinalyses were also made hourly for acetone and glucose. Fecal analyses were not made because of the short duration of the experiment. Gastric lavage was performed routinely within the first hour.

For purposes of presentation, the data were condensed to cover four periods. The number of hours elapsing between the onset of therapy and the end of each period is given for every case in table 1. The first period began with the onset of therapy and extended for an average of four to five hours. The second period corresponded roughly with the second four to five hours of therapy except in the phosphate group, for which the second period included only the interval from the beginning to the end of sodium phosphate administration. The third period extended from the eighth or ninth hour to the fourteenth to sixteenth hour of therapy. The fourth period covered the remaining time up to the termination of the study between the twenty-third and twenty-fourth hour. Clinical observations and results of blood analyses recorded in the tables represent values obtained at the end of the corresponding period. All values for intake, urinary output and balance for each period are recorded in terms of grams, milligrams or cubic centimeters per hour for purposes of comparing data in periods of unequal length.

Although the discussion of the effects of sodium phosphate will be reserved for another paper, it was convenient to present the data on the patients receiving it in the same tables with the data on the saline and dextrose groups. Since the treatment of the phosphate group in the first period was similar to that of the dextrose group, these two groups will be taken as a unit for the duration of the first period. Thereafter, only the dextrose group will be contrasted with the saline group.

For fatality rates and for data on the rate of disappearance of acetonuria the study was extended to include a total of 71 cases.

STATUS OF THE PATIENTS ON THEIR ADMISSION TO THE HOSPITAL

All patients had severe diabetic acidosis. The significant clinical and laboratory findings on their admission to the hospital are summarized in tables 1, 2 and 3. Carbon dioxide–combining power averaged 13.4

8. Benedict, S. R.: The Detection and Estimation of Glucose in the Urine, J. A. M. A. **57**:1192 (Oct. 7) 1911.

9. Hawk, P. B., and Bergeim, O.: Practical Physiological Chemistry, ed. 11, Philadelphia, P. Blakiston's Son & Co., 1937, p. 768.

10. Koch, F. C., and McMeekin, T. L.: A New Direct Nesslerization Microkjeldahl Method and a Modification of the Nessler-Folin Reagent for Ammonia, J. Am. Chem. Soc. **46**:2066, 1924.

TABLE 1.—*Clinical Status*

Group	Case	Experimental Periods Hours Elapsed from Admission to End of Period 1	2	3	4	Age, Yr.	Complications * on Admission	Mental State * at End of Period: Admission	1	2	3	4	Blood Pressure at End of Period: Admission	1	2	3	4	Severity Index, %	Deaths
Saline.....	1	4.00	8.00	16.00	24.00	43	1	1	1	1	1	0	140/90	130/90	140/90	140/90	140/90	15	—
	2	5.50	10.50	17.50	24.00	30	1	1	1	1	1	2	120/84	—	—	—	110/80	14	—
	3	4.00	10.00	16.00	24.00	26	0	2	2	0	0	0	86/74	80/64	90/70	90/70	90/70	15	—
	4	6.00	10.00	16.00	24.00	28	1	3	2	2	1	0	140/80	110/75	110/40	112/54	110/70	30	—
	5	4.50	6.50	12.50	24.00	39	0	1	1	1	1	0	100/80	104/70	104/70	98/60	90/70	10	—
	6	5.50	—	—	—	55	4	4	4	—	—	—	130/90	136/76	—	—	—	64	D
	7	6.00	13.00	18.50	24.00	17	1	2	1	1	0	0	128/80	100/75	—	120/80	—	19	—
Average.....		5.07	9.67	16.08	24.00	34	1.1	2.0	1.7	1.0	0.7	0.3	121/83	110/75	111/69	112/77	108/76	24	14%
Dextrose.....	8	5.00	8.00	11.50	18.50	67	4	4	4	4	3	4	0/0	70/40	70/50	60/40	56/40	82	D
	9	5.75	10.50	16.00	24.00	26	1	1	0	0	0	0	118/70	116/70	60/30	110/72	104/70	17	—
	10	4.00	7.50	12.50	—	51	4	3	3	1	3	—	85/65	110/60	106/58	58/28	—	61	D
	11	4.00	10.00	18.00	24.00	32	1	1	1	1	1	1	140/100	136/82	112/92	112/92	112/92	11	—
	12	4.00	8.00	16.00	24.00	65	0	2	2	1	0	0	108/50	152/60	—	140/70	140/64	31	—
	13	5.25	8.25	17.00	—	30	2	4	4	4	4	—	60/40	84/44	90/30	84/24	—	55	D
	14	6.00	10.00	17.00	23.50	40	3	4	4	4	4	4	116/74	130/0	118/85	125/80	110/70	57	D
	15	4.00	8.00	16.00	24.00	37	2	2	2	1	0	0	110/60	130/75	—	108/72	120/80	37	—
	16	3.00	6.33	17.00	24.00	20	0	2	2	2	1	0	120/80	120/78	120/80	120/10	118/80	13	—
	17	4.00	8.00	17.00	—	31	0	3	2	1	1	1	130/90	128/68	135/80	118/78	125/80	20	—
	18	4.00	8.00	16.00	24.00	18	3	1	1	1	1	0	120/80	—	—	—	—	27	—
Average.....		4.45	9.30	15.82	23.25	37.9	1.8	2.5	2.3	1.8	1.6	1.1	112/72	117/58	103/74	104/57	109/71	37	36%
Phosphorus....	19	3.17	4.17	16.00	24.00	28	0	4	4	1	1	0	130/80	105/65	98/58	112/54	110/70	30	—
	20	3.50	4.50	—	—	31	3	3	2	1	—	—	130/90	108/60	130/58	—	—	43	D
	21	6.25	7.75	16.00	20.50	14	1	3	2	0	0	0	84/64	90/20	104/64	102/60	102/60	43	—
	22	3.33	4.50	12.25	24.00	69	0	1	1	1	0	0	104/70	80/60	130/60	110/70	115/75	20	—
	23	3.50	4.75	11.00	24.00	39	0	3	2	1	1	0	104/78	95/75	104/64	95/60	105/65	25	—
	24	5.75	10.25	13.50	20.50	41	3	4	2	1	1	4	120/58	170/80	180/78	—	—	55	D
	25	8.50	13.50	17.50	24.00	35	3	4	2	0	0	0	118/70	120/80	150/80	130/70	130/80	56	—
	26	4.25	6.75	15.33	—	62	3	4	2	2	3	—	50/40	104/70	117/82	80/40	—	71	D
	27	4.00	8.25	12.00	24.00	26	2	2	3	1	1	0	138/84	100/60	104/68	102/72	118/70	28	—
	28	5.67	7.75	11.50	24.00	22	1	3	3	2	2	1	90/0	98/58	108/64	110/70	95/65	48	—
Average.....		4.79	7.23	13.90	23.13	36.7	1.6	3.1	2.1	1.0	1.0	0.7	107/64	107/63	123/68	105/62	111/69	42	30%

* Graded 0 to 4 as explained in the text.

TABLE 2.—*Status Before Treatment, Divided According to Therapeutic Regimen*

Group	No. of Cases	Age, Yr.	Mental State	Complications on Admission	Blood Pressure	Severity Index, %	Blood Sugar, Mg. %	Carbon Dioxide-Combining Power, Vol. %	Plasma Chloride, Mg. %	Hematocrit Reading	Specific Gravity	Plasma Phosphorus, Mg. %
Saline	7	34	2.0	1.1	121/83	24	501	16.1	485	54.7	1.033	8.9
Dextrose	11	37.9	2.5	1.8	112/72	37	457	14.0	496	54.7	1.029	7.9
Phosphate	10	36.7	3.1	1.6	107/64	42	495	11.7	501	54.1	1.031	7.2
Average	28	37.8	2.6	1.6	113/70	35	482	13.4	494	54.3	1.031	7.87

TABLE 3.—*Status Before Treatment, Divided According to Survival*

Group	No. of Cases	Age, Yr.	Mental State (0 to 4)	Complications on Admission	Blood Pressure	Severity Index, %	Blood Sugar, Mg. %	Carbon Dioxide-Combining Power, Vol. %	Plasma Chloride, Mg. %	Hematocrit Reading	Specific Gravity	Plasma Phosphorus, Mg. %
Survivors	20	34.1	2.1	3.3	122/75	25	474	13.8	499†	54.8	1.031	7.1
Dead	8	49.6	3.8	0.9	91/60	62	504	12.4	483*	53.6	1.031	8.7
Average	28	37.8	2.6	1.6	113/70	35	482	13.4	494‡	54.3	1.031	7.9

* Seven cases. † Seventeen cases. ‡ Twenty-four cases.

volumes per cent on admission and exceeded 19 volumes per cent in only 2 cases.[11] The blood sugar ranged from 220 to 810 mg. per hundred cubic centimeters, averaging 480 mg. The reaction for glycosuria and acetonuria was graded 4 plus in all cases. The ages of the patients ranged from 14 to 69 years, averaging 37.8. The blood pressure was at shock levels in 7 cases and was below its customary level in 19 of the remaining 21.[12]

The complications have been graded 0 to 4 in terms of their danger to the life of the patient. Thus, a grade of 4 was assigned to case 6 because of a combination of a huge infected postmammectomy incision and hypertensive heart disease with auricular fibrillation, to case 8 because of hypertension complicated by hemiplegia, renal insufficiency and recent myocardial infarction and to case 10 because of arteriosclerotic heart disease, auricular tachycardia and left and right ventricular failure. These complications were classified as grade 3: lobar pneumonia and urethral stricture, case 14; postappendical pelvic abscess, case 18; eighth month pregnancy with probable toxemia, case 20; the tabetic form of dementia paralytica and hypertensive heart disease with left ventricular hypertrophy, case 24; bronchopneumonia and infected scalp wound, case 25, and advanced arteriosclerotic heart disease in case 26. A grade of 2 was assigned to case 13 because of staphylococcic otitis externa with cellulitis, to case 15 because of rheumatic mitral stenosis and insufficiency without failure and to case 27 because of streptococcic peritonsillar abscess. Such complications as infections of the upper respiratory tract, epididymitis with orchitis, mild infection of the urinary tract and mild essential vascular hypertension were classed as grade 1.

The state of consciousness was graded numerically as follows: conscious, grade 0; drowsy, grade 1; semiconscious, grade 2; unconscious, grade 3, and unconscious and unresponsive to painful stimuli, grade 4. Over one half (15) of the patients were unconscious (grade 3 or 4), 6 were semiconscious and 7 were merely drowsy.

All presented the clinical picture of dehydration. Twenty of the 28 had hemotocrit readings of 50 per cent or above, and 6 of the 8 with lower hematocrit readings were anemic. Nineteen had a plasma specific gravity of 1.030 or greater, while only 4 had a specific gravity below 1.028.

Thirteen had a blood chloride content (expressed as NaCl) below 500 mg. per hundred cubic centimeters, the lowest being 385 mg., and only 1 had a value over 545 mg.

11. Cases 3 and 9, in which the carbon dioxide-combining powers were 21 and 35 volumes per cent respectively, were included because of certain peculiarities in the course worth reporting.

12. In cases 1, 6, 11 and 20, in which the blood pressures on admission were near the upper limits of normal, there was definite evidence of antecedent hypertension.

Since the prognosis in diabetic coma depends on many factors, a method of grading the status on the patient's admission to the hospital was deemed essential to the evaluation of results from different therapeutic regimens. The method of Collen [13] was selected as the best guide to prognosis. Collen analyzed the relation of all the previously mentioned factors to the ultimate outcome and concluded that prognosis was influenced chiefly by the age, mental state, diastolic blood pressure and the presence of complications serious enough in themselves to threaten life. He derived the following formula as the most accurate representation of the fatality rate in his series:

$$\text{Severity index} = \frac{30\ (\text{mental state} + \text{complications}) + 50 + \text{age} - \text{diastolic B.P.}}{4}$$

The mental state was graded 0 to 4 as has been described. Complications were graded by Collen 0 to 5 in terms of their danger to the life of the patient.[14]

The severity index was determined for each patient in this series and varied from 3 to 82 per cent, averaging 35 per cent. Of the 10 patients in this series whose severity index was above 40 per cent, 8 died; of the 18 with severity indexes below 40 per cent, all recovered. The importance of the factors stressed by Collen in determination of the final outcome was borne out in this small series, as shown in table 3. Only 3 of the 9 patients over 40 years of age survived, whereas 17 of the 19 below 40 recovered. Four of the 6 patients whose blood pressures were at shock levels on admission to the hospital died.[15] Eight of the 15 unconscious patients died. All fatalities occurred in patients who were unconscious on admission. Despite the dire prognostic significance of the presence of unconsciousness, irreversible damage to the central nervous system did not seem to be the major cause of death, since 4 of the 8 patients who failed to react to painful stimuli on admission to the hospital regained consciousness and the other 4 responded to stimuli before they relapsed and died.

Although choice of therapeutic regimen was made at random, subsequent analyses revealed a distinct difference in the severity of the condition in the three groups. This was reflected in average severity indexes of 24 per cent for the saline group, 37 per cent for the dextrose group and 42 per cent for the phosphate group. The main differences between the groups lay in the depression of consciousness, the drop in diastolic blood pressure and the severity of complications, all of which

13. Collen, M. F.: Mortality in Diabetic Coma, Arch. Int. Med. **70**:347 (Sept.) 1942.

14. As stated previously, the complications in our series were graded 0 to 4 rather than 0 to 5 as in Collen's work.

15. The blood pressures in the remaining 4 fatal cases were probably at shock levels for the originally hypertensive patients involved.

were least in the saline group (table 1). The three groups differed only slightly with respect to age, initial blood sugar content, carbon dioxide–combining power, chloride and plasma inorganic phosphorus contents, hematocrit reading and specific gravity (table 2).

RESULTS

A. *Effect of Early Administration of Dextrose on Carbohydrate Metabolism.*—1. Blood Sugar (table 4): The blood sugar contents on admission of the patients to the hospital were high, exceeding 400 mg. per hundred cubic centimeters in all but 3 cases. In the saline group, the blood sugar level fell rapidly during the first five hours from an average of 501 mg. to 146 mg. with an average dose of 91.7 units of insulin per hour. On the other hand, when dextrose was given during the first period, the level fell merely from 480 to 429 mg. with an average dose of 101.5 units of insulin per hour.

Further analysis of the 21 cases in which the patients received dextrose early reveals that the blood sugar content rose during the first period in 8, underwent no significant change in 4, showed a transitory fall and a secondary rise in 4 and fell progressively in 5. The behavior of the blood sugar depended on the clinical condition of the patient as well as on the dose of dextrose administered during the first few hours. Ten patients received dextrose at the rates of 6 to 20 Gm. per hour during the first period. A progressive fall in the blood sugar level occurred in all 3 patients with a severity index below 30 on a mean hourly dextrose intake of 13.8 Gm. and an insulin dose of 84 units. On the other hand, a progressive fall in the blood sugar level occurred in only 2 of the 7 patients with a severity index above 30 on a mean hourly dextrose intake of 13.0 Gm. and an insulin dose of 101 units. Three of the 5 patients who failed to tolerate dextrose in doses of 6 to 20 Gm. per hour were admitted in circulatory collapse. Dextrose was given during the first period at rates exceeding 20 Gm. per hour to 11 patients, including 6 with severity indexes of 30 or below. Hyperglycemia was maintained in all 11 patients, 5 showing a further rise during the first period and 3 a secondary rise after a transitory fall.

The clinical course was uneventful in the 5 patients who showed a progressive fall in the blood sugar content despite the early administration of dextrose. On the other hand, the clinical course was unfavorable in 6 of the 8 patients with increasing hyperglycemia during the first period, in 2 of the 4 patients with a maintained plateau and in 3 of the 4 patients who showed a considerable secondary rise in the blood sugar level after a transitory fall. Of the 16 patients with increasing or maintained hyperglycemia, 7 died, and 4 others went into shock from three to nine hours after the institution of treatment but subsequently recovered. For 3 of the 4 patients who went into circulatory collapse (cases 9, 19 and 22) an

TABLE 4.—*Data Relating to the Saline, Dextrose and Phosphate Groups*

Group	Case	Blood Sugar at End of Period, Mg./100 Cc.					Insulin, Units per Hour During Period				Total 24 Hour Insulin Units	Carbon Dioxide-Combining Power at End of Period, Vol. %					Hours Until Urine Was Acetone Free
		Admission	1	2	3	4	1	2	3	4		Admission	1	2	3	4	
Saline	1	364	178	40	154	—	165	13	2	5	765	13	19	26	37	—	10
	2	616	142	254	254	222	36	0	15	6	333	19	63†	69†	69†	77†	14
	3	454	140	130	333	—	70	0	0	4	315	21	37	—	50	—	12
	4	500	133	60	135	190	113	23	0	0	790	19	17	28	35	35	16
	5	460	120	103	103	168	96	20	4	3	525	16	39	36	36	41	11
	6	640	210	—	—	—	109	—	—	—	(600)*	14	15	—	—	—	—
	7	476	102	80	—	—	53	30	11	0	588	11	28	33	—	—	12
Average		501	146	111	163	170	91.7	14.0	5.0	3.0	554	16.1	31.1	38.4	45.4	51.0	12.5
Dextrose	8	488	420	514	464	328	90	67	114	21	1,200	11	33	33	45	50	16
	9	408	572	338	214	120	47	70	55	45	1,260	35	30	30	33	40	16
	10	500	572	444	572	—	175	80	44	—	(1,200)*	13	12	19	26	—	14
	11	220	200	166	105	110	37	30	11	4	435	16	21	26	35	47	5
	12	546	376	560	570	370	66	43	46	58	1,265	14	14	17	19	30	23
	13	444	450	408	500	—	149	47	20	—	(1,035)*	6	14	12	33	—	10.5
	14	488	420	364	514	332	97	58	51	62	1,570	15	30	25	25	39	8
	15	404	522	444	168	—	63	29	14	6	520	11	16	30	49	—	14
	16	552	430	210	103	200	67	27	41	0	730	9	28	46	52	56	12
	17	476	470	400	200	—	109	46	22	—	(820)*	10	16	17	21	—	10
	18	500	—	410	266	266	63	58	36	4	895	14	—	46	50	50	6
Average		457	443	367	334	273	87.5	50.4	41.0	25.0	984	14.0	21.4	27.4	35.3	44.6	12.2
Phosphorus	19	420	412	—	296	67	123	130	71	16	1,435	12	29	—	42	48	11
	20	572	408	534	—	—	171	50	—	—	(650)*	14	10	18	—	—	—
	21	426	454	332	236	97	110	73	39	0	1,040	8	21	27	38	41	10.5
	22	312	354	308	222	151	60	129	26	22	810	19	19	24	26	36	11
	23	444	—	500	464	174	129	40	67	32	1,340	10	—	12	16	44	11
	24	444	490	320	364	—	117	72	42	34	1,370	13	25	46	43	—	14
	25	810	464	118	92	260	78	58	0	0	950	11	26	37	43	48	13
	26	454	500	500	374	66	141	80	48	—	(1,220)*	13	22	38	42	—	14
	27	616	266	284	308	66	148	59	13	10	1,005	9	24	29	35	48	12
	28	448	380	262	206	99	92	48	15	26	998	8	13	23	43	51	18
Average		495	414	351	285	129	116.9	73.9	35.6	17.5	1,125	11.7	21.0	28.2	36.5	45.1	13.3

* Not included in averages. The patients in cases 6, 10, 13, 20 and 26 died prior to period 4, and in case 17 no data were available for this period.
† This patient received 1,000 cc. of a 2 per cent solution of sodium bicarbonate in the first period.

uneventful course would have been anticipated in view of severity indexes between 17 and 30 per cent, and in the remaining case (21) a favorable course might have been expected in view of the patient's age. The experience with these cases does not imply that the early administration of dextrose is necessarily followed by circulatory failure or a stormy clinical course, since the patients in cases 12, 17 and 18 satisfactorily tolerated equivalent or larger doses. Nevertheless, in some of the cases, particularly 9, 19, 21 and 22, there appeared to be a correlation between the admin-

TABLE 5.—*Glucose Metabolism*

		Intake, Gm. per Hour. Period				Output, Gm. per Hour. Period				Balance, Gm. per Hour. Period			
Group	Case	1	2	3	4	1	2	3	4	1	2	3	4
Saline.....	1	0	3.1	10.9	0	2.1	0	0.3	1.2	— 2.1	+ 3.1	+10.7	— 1.2
	2	0	40.0	28.6	12.3	5.8	3.1	6.7	0.3	— 5.8	+36.9	+21.9	+12.0
	3	0	9.5	20.1	16.6	5.2	1.2	1.2	—	— 5.2	+ 8.3	+18.9	—
	4	0	0	30.8	40.0	6.7	3.2	0.7	0.5	— 6.7	— 3.2	+30.2	+39.6
	5	0	0	40.0	10.4*	2.3	0	2.8	—	— 2.3	0	+37.2	—
	6	0	—	—	—	1.4	—	—	—	— 1.4	—	—	—
	7	0	37.1	30.9	14.5	0.8	0	0.3	—	— 0.8	+37.1	+30.6	—
Average.....		0	15.0	26.9	17.4	3.5	1.2	2.0	0.6	— 3.5	+13.8	+24.9	+16.8
Dextrose.....	8	10.1	0	1.4	6.4	0	0	2.4	0.4	+10.1	0	— 1.0	+ 6.0
	9	59.2	38.9	56.4	38.8	26.8	20.4	17.6	14.1	+32.4	+18.5	+38.7	+24.6
	10	6.3	21.1	21.7	—	6.3	9.3	2.9	—	— 0.1	+11.8	+18.6	—
	11	12.5	30.0	31.3	8.3*	3.5	—	—	—	+ 9.0	—	—	—
	12	56.9	53.1	35.0	47.5	2.8	40.4	16.7	34.4	+54.1	+12.7	+18.3	+13.1
	13	20.0	0	10.3	—	4.3	1.2	0.3	—	+15.7	— 1.2	+10.0	—
	14	33.3	37.5	10.7	11.5	0.8	5.3	0.2	0.2	+32.5	+32.2	+10.5	+11.3
	15	28.8	42.5	23.1	36.3	6.8	13.1	5.3	1.3	+22.0	+29.4	+17.8	+35.0
	16	16.3	0	45.9	34.3	8.5	2.5	2.0	0.1	+ 7.8	— 2.5	+43.9	+34.2
	17	67.5	53.8	21.1	—	8.7	11.9	—	—	+58.8	+41.9	—	—
	18	50.0	75.0	42.4	8.7	17.2	31.0	15.5	1.7	+32.8	+44.0	+26.9	+ 7.0
Average.....		32.8	32.1	27.4	26.2	7.8	13.5	7.0	7.5	+25.0	+18.6	+20.4	+18.7
Phosphorus..	19	40.9	40.0	49.8	25.0	12.3	11.5	7.3	1.2	+28.6	+28.5	+42.5	+23.8
	20	28.5	25.0	—	—	10.0	6.0	—	—	+18.5	+19.0	—	—
	21	16.0	0	10.3	35.5	12.1	6.5	1.9	0.7	+ 3.9	— 6.5	+ 8.4	+34.8
	22	30.0	68.6	34.2	33.6	5.0	9.4	6.5	1.4	+25.0	+59.2	+27.7	+32.2
	23	28.5	0	37.0	4.0*	22.1	14.4	17.2	—	+ 6.4	—14.4	+19.8	—
	24	17.4	8.9	36.9	34.2	3.9	3.3	2.8	3.0	+13.5	+ 5.6	+34.1	+31.2
	25	11.8	0	40.0	49.2	6.8	2.2	0	0	+ 5.0	— 2.2	+40.0	+49.2
	26	35.2	0	41.9	—	13.6	13.1	3.9	—	+21.6	—13.1	+38.0	—
	27	12.5	49.3	34.6	25.8	4.9	7.5	7.7	1.6	+ 7.6	+41.8	+26.9	+24.2
	28	10.6	0	6.0	16.2	6.7	9.8	3.4	1.0	+ 3.9	— 9.8	+ 2.6	+15.2
Average.....		23.1	19.2	32.3	31.3	9.7	8.4	5.6	1.2	+13.4	+10.8	+26.7	+30.1

* Not included in average.

istration of dextrose during the first four hours, the maintenance of pronounced hyperglycemia and the unfavorable course.

The sharp contrast in the levels of the blood sugar in the saline and dextrose groups, which became evident in the first four to five hours, persisted throughout the rest of the study. The blood sugar content remained for the most part in the vicinity of normal in 5 of the 6 surviving patients of the saline group, even though insulin dosage was comparatively small, averaging 6.5 units per hour. On the other hand, hyperglycemia persisted throughout the entire period of observation in

7 of the 11 cases in the dextrose group and for most of the first twenty-four hours in 3 others in spite of relatively large doses of insulin averaging 42.3 units per hour. Of the 5 patients in whom the blood sugar was consistently above 300 mg. per hundred cubic centimeters, 4 died. Maintenance of pronounced hyperglycemia appeared to be partially responsible for the unfavorable clinical course.

2. Glycosuria (tables 5 and 6): From table 5 it is evident that the degree of glycosuria during each period was much greater in the dextrose

TABLE 6.—*Glucose Metabolism*

Group	Case	Intake, Total Gm. Period 1	Intake, Total Gm. Period 2+3+4	Output, Total Gm. Period 1	Output, Total Gm. Period 2+3+4	Balance, Total Gm. Period 1	Balance, Total Gm. Period 2+3+4
Saline	1	0	100.0	8.4	30.7	— 8.4	+ 69.3
	2	0	480.0	31.9	64.4	— 31.9	+415.6
	3	0	310.0	20.7	—	— 20.7	—
	4	0	505.0	40.0	20.2	— 40.0	+484.3
	5	0	360.0	10.5	—	— 10.5	—
	6	0	—	7.9	—	— 7.9	—
	7	0	510.0	4.5	—	— 4.5	—
Average		0	377.5	17.7	38.4	— 17.7	+322.7
Dextrose	8	50.0	50.0	0.0	11.4	+ 50.0	+ 38.6
	9	340.0	805.0	154.7	309.0	+183.3	+496.0
	10	25.0	—	25.3	—	— 0.3	—
	11	50.0	480.0	14.0	—	+ 36.0	—
	12	227.5	872.5	11.3	570.2	+216.2	+302.3
	13	105.0	—	22.8	—	+ 82.2	—
	14	200.0	300.0	4.6	6.5	+195.4	+293.5
	15	115.0	645.0	27.1	23.9	+ 87.9	+621.1
	16	49.0	729.0	25.4	32.5	+ 23.6	+690.5
	17	270.0	—	34.8	—	+235.2	—
	18	200.0	710.0	68.5	251.7	+131.5	+458.3
Average		148.3	549.2	35.3	159.3	+113.0	+415.2
Phosphorus	19	130.0	830.0	38.9	107.8	+ 91.1	+722.2
	20	100.0	—	35.0	—	+ 65.0	—
	21	100.0	240.0	75.8	28.4	+ 24.2	+211.6
	22	100.0	740.0	16.8	77.8	+ 83.2	+662.2
	23	100.0	283.0	77.6	—	+ 22.4	—
	24	100.0	400.0	22.2	44.8	+ 77.8	+355.2
	25	100.0	480.0	57.7	10.9	+ 42.0	+469.1
	26	150.0	—	58.0	—	+ 92.0	—
	27	50.0	650.0	19.5	80.4	+ 30.5	+569.6
	28	60.0	225.0	37.8	146.0	+ 22.2	79.0
Average		99.0	481.0	43.9	70.9	+ 55.1	+438.4

group than in the saline group. A comparison of the two groups during the third period reveals that the greater glycosuria in the dextrose group cannot be attributed exclusively to the higher intake. During this period this group received an average of 27.4 Gm. per hour and excreted 7.0 Gm. per hour, or 26 per cent, whereas the saline group received 26.9 Gm. per hour and excreted only 2.0 Gm. per hour, or 7 per cent of the intake. The difference in the degree of glycosuria was due chiefly to the fact that the blood sugar level from the beginning to the end of this period was markedly elevated in the dextrose group (ranging from 367 to 334 mg.

per hundred cubic centimeters) and was nearly normal in the saline group (ranging from 111 to 163 mg. per hundred cubic centimeters). The degree of glycosuria was proportional to the blood sugar level except in the presence of shock or oliguria. Thus the early administration of dextrose maintained the blood sugar at high levels and thereby predisposed the patients to severe glycosuria.

3. Glucose Retention (tables 5 and 6): Glucose retention represents the difference between the intake and the urinary excretion. The figure for retention does not indicate the fate of the retained glucose and thus includes (1) glucose which had been oxidized, (2) that stored as glycogen and (3) that retained unchanged.

During the first period the group receiving no dextrose excreted an average of 3.5 Gm. per hour and therefore exhibited a similar negative balance. The remaining patients received an average of 28.2 Gm. per hour, of which 19.5 Gm. was retained. Since the average blood sugar level had fallen slightly in these cases, it is apparent that glucose was being oxidized or stored in the tissues at a rate approximating 20 Gm. per hour. It is noteworthy that the patients in cases 12 and 17 were retaining glucose at a maximum rate for human beings[16] despite the presence of severe diabetic acidosis.

During the second, third and fourth periods, the saline group received an average of 20.5 Gm. of dextrose per hour and retained 19.2 Gm., or 94 per cent, on an average insulin dose of 6.5 units per hour, whereas the dextrose group received 28.8 Gm. per hour and retained 20.1 Gm., or only 70 per cent, on an average insulin dose of 34.1 units per hour. The saline group retained 2.6 Gm. of glucose per unit of insulin, while the dextrose group retained only 0.6 Gm. per unit of insulin. Since the question might arise as to whether the much more efficient utilization in the saline group might be explained by the smaller glucose load, attention should again be directed to the third period when the dextrose intake of the two groups was nearly equal. During this period the saline group received 26.9 Gm. and retained 24.9 Gm., or 93 per cent, on an average insulin dose of 5 units per hour, whereas the dextrose group received 27.4 Gm. and retained only 20.4 Gm., or 74 per cent, on an average insulin dose of 41 units per hour. The dextrose insulin ratio during this period was almost 5 Gm. per unit in the former and 0.5 Gm. per unit in the latter. Thus, the early administration of dextrose, by maintaining pronounced hyperglycemia and glycosuria, resulted in less efficient utilization of exogenous glucose.

The foregoing observations do not imply that the level of blood and urinary glucose is the only factor governing the efficiency of glucose

16. Woodyatt, R. T.; Sansum, W. D., and Wilder, R. M.: Prolonged and Accurately Timed Intravenous Injections of Sugar: A Preliminary Report, J. A. M. A. **65**:2067 (Dec. 11) 1915.

utilization. Additional factors are revealed through a comparison of individual cases. For example, a study of cases 13 and 18 reveals almost identical blood sugar levels at the onset of the third period (408 and 410 mg. per hundred cubic centimeters respectively) but considerable difference in carbohydrate metabolism during the period. In case 18 the blood sugar level fell to 266 mg. despite retention of 26.9 Gm. per hour on a dose of 36 units of insulin per hour. In case 13 the blood sugar level rose to 500 mg. in the face of retention of only 10 Gm. of glucose per hour on a dose of 20 units of insulin per hour in the third period. The rise in blood sugar in case 13 would indicate that a portion of the retained glucose was not metabolized. The patient in this case was moribund at the time and well illustrates the decided carbohydrate intolerance of patients in poor clinical condition.

B. *Effect of Early Administration of Dextrose on Acidosis.*—The hourly urinalyses for acetone performed in all cases provided an index of the rate of disappearance of ketosis. The time required for the urine

TABLE 7.—*Disappearance of Acetonuria, Averages for Seventy-One Cases*

Group	Total Cases	Died While Acetonuria Was Still Present	Percentage Who Died While Acetonuria Was Still Present	Time in Which Urine Became Acetone Free, Hr.
Saline	22	2	9	11.5
Dextrose	33	6	18	11.8
Phosphate	16	2	13	11.9

to become acetone free averaged 12.5 hours in the saline group and 12.2 hours in the dextrose group (table 4). Furthermore, acetonuria did not disappear faster in patients who retained more than 20 Gm. of glucose per hour than in those who retained lesser quantities. Because of the absence of significant differences in this small series, observations were extended over a total of 47 patients who lived long enough to become acetone free (table 7). The time required for the urine to become acetone free averaged 11.5 hours in the 20 patients receiving saline and 11.8 hours in the 27 receiving dextrose. The groups were comparable as judged by the severity index. Therefore, the maintenance of hyperglycemia by the early administration of dextrose did not significantly alter the rate of disappearance of acetone from the urine. Reference to the carbon dioxide–combining power in table 4 offers further confirmation for the conclusion that acidosis did not disappear more rapidly in the dextrose group than in the saline group.

C. *Effect of Early Administration of Dextrose on Chloride and Water Metabolism* (tables 8 to 11).—On their admission to the hospital the saline and dextrose groups were closely comparable as to blood chloride content (485 versus 496 mg. per hundred cubic centimeters),

TABLE 8.—*Water Metabolism*

Group	Case	Fluid Intake, Cc. per Hr. Period 1	2	3	4	Fluid Output, Cc. per Hr. Period 1	2	3	4	Fluid Balance, Cc. per Hr. Period 1	2	3	4	Hematocrit Reading, Vols. % Period Admission	1	2	3	4
Saline.....	1	750	563	219	0	143	78	51	151	+607	+485	+168	−151	54.3	—	47.8	44.3	48.4
	2	182	380	236	102	200	59	121	27	− 18	+271	+115	+ 75	58.0	—	50.5	50.9	50.9
	3	500	324	323	155*	198	58	63	—	+302	+266	+260	—	66.6	51.8	44.2	46.5	43.7
	4	583	125	303	330	193	145	121	126	+390	− 20	+182	+204	49.6	35.3	39.3	41.3	35.4
	5	500	000	655	86	93	35	118	77	+407	+565	+537	+ 9	48.3	39.2	29.4	36.0	36.4
	6	545	—	—	—	73	—	—	—	+472	—	—	—	48.0	39.2	—	—	—
	7	333	617	362	302	145	57	52	95	+188	+560	+310	+207	58.0	49.0	37.2	—	—
Average.....		484	427	350	164	149	72	88	95	+335	+355	+262	+ 69	54.7	42.9	41.4	43.8	43.0
Dextrose.....	8	782	133	57	157	0	0	84	6	+782	+133	− 27	+151	56.8	45.0	45.5	44.2	41.3
	9	694	491	664	393	381	262	194	197	+313	+229	+470	+196	49.0	42.0	36.0	—	—
	10	413	458	436	—	215	277	91	—	+198	+181	+345	—	56.0	47.0	40.0	44.5	—
	11	333	445	331	167	98	254	151	101	+235	+191	+180	+ 66	53.0	52.0	41.0	40.0	43.0
	12	768	643	626	626	85	890	709	613	+683	−247	− 83	+ 13	54.2	48.6	52.1	54.7	43.9
	13	590	0	232	—	151	30	12	—	+439	− 30	+220	—	61.5	47.7	49.0	39.8	—
	14	917	750	357	385	17	110	50	54	+900	+640	+307	+331	58.0	41.5	44.7	45.0	35.3
	15	708	498	215	360	194	238	128	88	+514	+260	+ 87	+272	48.0	42.0	40.0	42.0	42.0
	16	420	420	483	404	180	180	60	37	+240	+240	+423	+367	58.0	48.3	41.2	44.1	38.0
	17	760	605	321*	—	300	358	—	—	+460	+247	—	—	—	—	—	—	—
	18	625	525	202	63	343	398	182	170	+282	+127	+ 80	−107	58.0	41.7	38.8	43.7	43.3
Average.....		637	452	366	319	179	272	166	158	+458	+180	+200	+161	54.7	45.6	42.8	44.2	41.0
Phosphorus...	19	836	830	603	206	378	345	145	123	+458	+485	+458	+ 83	55.7	43.2	42.1	35.3	36.5
	20	571	1,000	—	—	314	205	—	—	+257	+795	—	—	52.0	42.0	43.0	—	—
	21	480	333	201	146	185	133	44	25	+295	+200	+157	+121	58.0	45.6	43.7	40.6	36.4
	22	600	996	384	351	117	157	105	119	+483	+839	+279	+232	53.0	44.2	40.0	38.2	34.7
	23	1,000	400	590	223	394	228	258	46	+606	+172	+332	+177	49.3	35.6	40.0	35.7	34.3
	24	522	296	304	383	140	137	98	86	+382	+159	+206	+297	55.6	41.6	40.2	38.2	—
	25	353	200	330	407	137	63	15	13	+216	+137	+315	+394	47.7	45.2	37.3	35.7	32.6
	26	1,175	400	645	—	392	468	114	—	+783	− 68	+531	—	47.0	36.6	37.2	35.6	—
	27	875	898	443	359	195	226	217	68	+680	+672	+226	+291	63.9	—	42.0	41.3	44.6
	28	458	479	253	244	130	163	109	61	+328	+316	+144	+183	58.7	49.3	38.9	44.0	36.9
Average.....		687	583	417	290	238	213	123	68	+449	+370	+294	+222	54.1	42.6	40.4	38.3	36.6

* Excluded from average.

TABLE 9.—*Chloride Metabolism*

Group	Case	Plasma Chloride,† Mg./100 Cc. Period: Admission	1	2	3	4	Chloride Intake,‡ Gm. per Hr. Period: 1	2	3	4	Chloride Output,‡ Gm. per Hr. Period: 1	2	3	4	Chloride Balance,‡ Gm. per Hr. Period: 1	2	3	4
Saline	1	543	603	585	582	591	4.09	3.07	1.19	0	0.28	0.59	0.17	0.30	+3.82	+2.48	+1.02	−0.30
	2	476	509	512	464	—	0	0	0	0	0.04	0.02	0.05	0.01	−0.04	−0.02	−0.05	−0.01
	3	447	574	—	524	547	2.73	0.59	0	0*	0.11	0.04	0.06	—	+2.62	+0.55	−0.006	—
	4	471	564	586	550	532	3.18	0.68	0.46	0	0.24	0.42	0.55	0.68	+2.94	+0.26	−0.09	−0.68
	5	474	537	597	543	603	2.04	2.73	1.46	0	0.05	0.09	0.27	0.28	+1.99	+2.64	+1.19	−0.28
	6	501	626	—	—	—	2.97	—	—	—	0.11	—	—	—	+2.86	—	—	—
	7	486	568	—	—	—	1.81	0.78	0.99	0.99*	0.11	0.19	0.80	—	+1.70	+0.59	+0.19	—
Average		485	569	570	533	568	2.40	1.31	0.68	0	0.13	0.23	0.32	0.32	+2.27	+1.08	+0.36	−0.32
Dextrose	8	531	546	546	555	570	2.51	0.24	0.13*	0.56*	0	0	—	—	+2.51	+0.24	—	—
	9	450	—	—	—	—	1.90	1.52	1.32	0	0.45	0.31	0.34	0.42	+1.45	+1.21	+0.98	−0.42
	10	439	579	615	615	—	2.02	1.92	1.09	—	0.08	0.18	0.05	—	+1.94	+1.74	+1.04	—
	11	—	510	558	528	507	1.36	1.82	0.68	0.91	0.14	0.88	0.57	0.38	+1.22	+0.94	+0.11	+0.53
	12	501	501	501	483	585	2.38	1.71	1.36	2.05	0.08	1.08	0.47	0.86	+2.30	+0.63	+0.89	+1.19
	13	537	597	624	585	—	2.70	0	0.62	—	0.14	0.05	0.02	—	+2.56	−0.05	+0.60	—
	14	385	471	498	506	585	2.73	4.09	1.69	0.98	0.01	0.05	0.03	0.03	+2.72	+4.04	+1.66	+0.95
	15	—	—	—	534	—	2.73	0.68	0.34	0	0.01	0.02	0.02	0.02	+2.72	0.66	+0.32	−0.02
	16	512	581	615	604	597	2.12	2.12	0.70	0	0.05	0.05	0.19	0.05	+2.07	+2.07	+0.51	−0.05
	17	627	597	597	597	—	2.73	1.50	1.15*	—	0.20	0.49	—	—	+2.53	+1.01	—	—
	18	481	525	525	528	555	2.73	1.36	0	0	0.13	0.46	0.22	0.01	+2.60	+0.90	−0.22	−0.01
Average		496	545	564	554	567	2.36	1.54	0.87	0.56	0.12	0.32	0.21	0.25	+2.24	+1.22	+0.66	+0.31
Phosphorus	19	492	543	558	570	522	3.44	0	1.07	0	0.27	0.24	0.30	0.24	+3.17	−0.24	+0.77	−0.24
	20	456	558	—	—	—	3.12	2.72	—	—	0.35	0.45	—	—	+2.77	+2.27	—	—
	21	471	588	608	638	656	2.03	0	0	0	0.22	0.27	0.21	0.38	+1.81	−0.27	−0.21	−0.38
	22	534	597	597	585	572	3.28	0	0.23	0.47	0.17	0.38	0.25	0.58	+3.11	−0.38	−0.02	−0.11
	23	513	—	621	591	618	5.19	0	1.18	0.63	0.48	0.23	0.35	0.29	+4.71	−0.23	+0.83	+0.34
	24	—	556	594	586	—	2.21	0	0	0	0.23	0.26	0.17	0.12	+1.98	−0.26	−0.17	−0.12
	25	506	626	620	606	594	1.92	0	0	0	0.13	0.13	0.02	0.08	+1.79	−0.13	−0.02	−0.08
	26	534	585	597	591	—	5.33	0	0.85	—	0.76	1.45	0.23	—	+4.57	−1.45	+0.62	—
	27	—	—	581	558	543	2.79	0.41	0	0.46	0.05	0.21	0.37	0.18	+2.74	+0.20	−0.37	+0.28
	28	498	591	621	701	646	2.04	0	0.61	0.52	0.06	0.09	0.13	0.11	+1.98	−0.09	+0.48	+0.41
Average		501	581	597	603	593	3.14	0.31	0.44	0.26	0.27	0.37	0.23	0.24	+2.87	−0.06	+0.21	+0.02

* Not included in average.
† Expressed as NoCl.
‡ Expressed as Cl.

hematocrit reading (each 54.7 per cent) and clinical degree of dehydration. During the first period the average intake and output of chloride was almost identical in the two groups (table 9). The fact that both groups retained 95 per cent of the chloride administered during this period is a reflection of the considerable chloride depletion which occurred prior to the advent of therapy. The water intake was higher in the dextrose group, but the percentage excreted during the first period was almost the same in the two groups (table 11). The volume of urine was directly proportional to the amount of glucose excreted. When values for the fluid output for the first period were plotted against those for glucose output, a straight line graph was obtained.

During the second period, the saline and dextrose groups had a comparable intake of fluid (427 versus 452 cc. per hour [table 8]) and chloride (1.31 versus 1.54 Gm. per hour [table 9]). Nevertheless, a great disparity developed between the groups in the handling of water and chloride (table 11). Water output averaged 60 per cent of the intake in the dextrose group and only 17 per cent of the intake in the saline group. The high urinary volume in the dextrose group was the direct consequence of the persistent hyperglycemia with its attendant glycosuria. In spite of the intensive diuresis in the dextrose group, a positive fluid and chloride balance was maintained, and a hemodilution comparable to that of the saline group was achieved.

The question arises of the disposition of the retained water and chloride in the two groups of cases. In the absence of measurements of plasma and interstitial and intracellular fluid volumes, indirect evidence must be utilized in the analysis of water and electrolyte retention. The following calculations are based on the generally accepted idea that chloride is almost exclusively an extracellular ion and that the concentration of chloride in interstitial fluid is the same as that in the plasma.[17] When the concentration of chloride in the fluid retained during a given period and the plasma chloride level at the beginning and end of the period are known, the direction of the shift of water between intracellular and extracellular spaces may be predicted.[18] For example, if the retained fluid is hypotonic in respect to chloride and the plasma chloride does not change, the surplus water presumably shifts into the cells. On the other hand, if the retained fluid is hypertonic in chloride content and the plasma level remains constant, the water deficit is

17. Darrow, D. C., and Yannett, H.: Changes in Distribution of Body Water Accompanying Increase or Decrease in Extracellular Electrolyte, J. Clin. Investigation **14**:226, 1935. Peters, J. P.: Body Water, Springfield, Ill., Charles C Thomas, Publisher, 1935, p. 132.

18. Darrow, D. C., and Yannett, H.: Changes in Distribution of Body Water Accompanying Increase or Decrease in Extracellular Electrolyte, J. Clin. Investigation **14**:266, 1935.

presumably made up by shift of intracellular water to interstitial spaces and plasma. A rise in plasma chloride content accompanying retention of hypertonic solution will account for a portion, if not all, of the surplus chloride.

During the first period, both the saline and glucose groups showed a considerable rise in plasma chloride content while they were retaining

TABLE 10.—*Chloride Concentrations (Milligrams Per Hundred Cubic Centimeters)**

Group	Plasma	Administered Fluid	Retained Fluid
Admission			
Saline	304	...	...
Dextrose	310	...	...
Phosphorus	313	...	...
Period 1			
Saline	346	485	667
Dextrose	331	370	448
Phosphate	352	458	639
Period 2			
Saline	346	307	304
Dextrose	342	341	678
Phosphate	364	53†	Negative Cl balance;† positive H_2O balance
Period 3			
Saline	323	194	137
Dextrose	336	238	330
Phosphate	366	106	71
Period 4			
Saline	344	No Cl intake	Negative Cl balance; positive H_2O balance
Dextrose	344	175	193
Phosphate	360	90	9

* The concentration of chloride in the fluids was determined as follows:

(1) In "administered fluid" = $\frac{\text{Chloride (mg.) administered}}{\text{Fluid (cc.) administered}}$

(2) In "retained fluid" = $\frac{\text{Chloride (mg.) administered} - \text{chloride (mg.) excreted}}{\text{Fluid (cc.) administered} - \text{fluid (cc.) excreted}}$

† Only two patients were given chloride.

TABLE 11.—*Percentage of Excretion of Administered Fluid and Chloride*

Period	Saline Group		Dextrose Group		Phosphate Group	
	Water	Chloride	Water	Chloride	Water	Chloride
1	31	5	29	5	35	9
2	17	18	60	21	37	(119)*
3	25	47	45	24	30	52
4†	58	..	50	49	23	92

* Negative chloride balance.
† No chloride intake.

hypertonic fluid. The rise in the plasma chloride content was sufficiently great in both groups to account for the surplus chloride retained.

During the second period the saline group received and retained a slightly hypotonic solution (table 10). Since the plasma chloride content remained constant, the surplus water apparently passed into the cells. On the other hand, the dextrose group received isotonic solution

of chloride but retained fluid that was markedly hypertonic in respect to chloride. The high chloride concentration of the retained fluid was a consequence of the polyuria provoked by the intense glycosuria. Despite the retention of 873 cc. of fluid with a chloride concentration twice that of the plasma, the blood chloride level rose only 11 mg. per hundred cubic centimeters. The retention of so much excess chloride with so little rise in the plasma level indicated a shift of water into interstitial spaces and plasma out of cells that were already markedly dehydrated. This conclusion is borne out by the fact that the dextrose group underwent more hemodilution than the saline group during the second period even though their fluid retention was 826 cc. less.

D. *Effect of the Early Administration of Dextrose on the Outcome.*—Since the clinical status in diabetic coma has so important an influence on the outcome, the severity of the condition on the patient's admission to the hospital was taken as a basis for the evaluation of therapeutic results. The 7 patients of the saline group had an average severity index of 24 per cent and an actual fatality rate of 14 per cent, while the 11 patients receiving dextrose early had a severity index of 37 per cent and an actual fatality rate of 36 per cent. Inasmuch as these figures were not significant because of the small number of patients and the disparity in status on their admission to the hospital, the study was broadened to include all patients with diabetic coma admitted between July 1943 and April 1946. The series comprised a total of 71 patients. Sixteen of these received sodium phosphate and will be considered separately in another paper. For 22 of the remaining patients, from whom dextrose was withheld for at least the first four hours, the mean severity index was 40 per cent and the actual fatality rate was 36 per cent. The other 33 patients received dextrose during the first four hours and had a mean severity index of 37 per cent but a fatality rate of 52 per cent. From these averages, it would appear that the early administration of dextrose had an unfavorable effect on the outcome from diabetic coma.

An analysis of individual cases revealed that no patients with a severity index over 60 per cent survived whereas only 1 with an index below 30 per cent died.[19] These figures are in accord with Collen's statistics, which revealed only two recoveries among 25 patients with an index over 60 per cent and four deaths among 28 patients with an index below 20 per cent.[13] Whereas practically all patients with an index below 30 per cent recover and practically all those with an index over 60 per cent succumb, the outcome in the intervening group would be expected to reflect more closely the effect of the therapeutic regimen.[18] Therefore,

19. This patient was treated with 1,000 cc. of a 5 per cent solution of dextrose subcutaneously, a procedure known to cause depletion of body electrolytes by localizing them at the site of dextrose infusion.

the results were analyzed in our patients with a severity index between 30 to 60 per cent. Among the 7 patients of this group who received no dextrose during the first four hours the mean severity index was 38 per cent and the fatality rate was 43 per cent. Among the 18 patients of this group who were treated with dextrose early the mean severity index was 44 per cent but the fatality rate was 67 per cent. Thus, in groups of comparable severity better results were obtained when dextrose was withheld during the first four hours than when it was administered during this period.

COMMENT

With the advent of insulin, specific treatment of diabetic acidosis became feasible. Improvement in results has followed the recognition of the need for massive doses of insulin [20] and for restoration of losses of sodium chloride and water.[21] It has also been claimed that the adminis-

TABLE 12.—*Effect of Therapy on Seventy-One Successive Cases of Diabetic Acidosis*

Group	Number	Dead *	Actual Fatality Rate, %	Severity Index, %
A. Severity Index 3 to 82 per Cent				
Saline	22	8	36	40
Dextrose	33	17	52	37
Phosphate	16	6	37	46
Total	71	31	44	40
B. Severity Index 30 to 60 per cent				
Saline	7	3	43	38
Dextrose	18	12	67	44
Phosphate	11	3	27	44

* Three patients who died three to twenty-one days later were not considered to have died in coma.

tration of dextrose in liberal amounts during the early hours of treatment is a beneficial procedure.[22] Much controversy has arisen over this state-

20. Root, H. F.: The Use of Insulin and Abuse of Glucose in the Treatment of Diabetic Coma, J. A. M. A. **127**:557 (March 10) 1945; correction, ibid. **127**:1068 (April 21) 1945.

21. Danowski, T. S.; Winkler, A. W., and Peters, J. P.: Salt Depletion, Peripheral Vascular Collapse, and the Treatment of Diabetic Acidosis, Yale J. Biol. & Med. **18**:405, 1946.

22. (*a*) Himsworth, H. P.: The Role of Glucose in the Treatment of Diabetic Intoxication, Lancet **2**:165, 1932. (*b*) Lawrence, R. D.: Treatment of Diabetic Coma, Brit. M. J. **2**:81, 1936. (*c*) Soskin, S., and Levine, R.: Carbohydrate Metabolism, Chicago, University of Chicago Press, 1946, p. 281. (*d*) Butler, A. M., in discussion on Diabetes Mellitus with Acidosis, Cabot Case 30451, New England J. Med. **231**:657, 1944. (*e*) Conn, J., and Bauer, J. M.: The Administration of Glucose in the Treatment of Diabetic Coma, Univ. Hosp. Bull., Ann Arbor **11**:49, 1945. (*f*) Peters, J. P.: Starvation Diabetes, Yale J. Biol. & Med. **17**:705, 1944; The Use of Carbohydrate in Diabetic Acidosis, Am. J. Digest. Dis. **13**:127, 1946.

ment, and the arguments pro and con will be given before proceeding with a discussion of our results.

The arguments in favor of early administration of dextrose are based principally on animal studies showing that hyperglycemia apparently favors glucose oxidation, glycogen deposition and abolition of ketosis. Peters [23] and Butler [22d] stated that combustion of carbohydrate is promoted by hyperglycemia. The apparent basis for this is work by Soskin showing that the depancreatized, hepatectomized animal can utilize large amounts of carbohydrate without insulin, provided that the blood sugar is maintained at high levels.[1] Mirsky [24] found that ketosis is diminished or abolished in depancreatized animals or in human beings with diabetic acidosis when a sufficient quantity of carbohydrate is given. These observations have been interpreted to mean that forced carbohydrate administration is beneficial in diabetic coma. Further justification for the early use of dextrose has been attempted by Soskin and Levine, who calculated a potential carbohydrate deficit of approximately 500 Gm. prior to treatment.[22c]

Root, a leading opponent of the early use of dextrose, advised withholding it until the fourth to the sixth hour of treatment or until evidence of normal utilization of carbohydrate is present.[20] He moderated his strong opposition by stating that "no one supposes that in coma the administration of perhaps 10 grams per hour would be harmful, providing a sufficient amount of insulin had been given to make possible its normal utilization."[25] He opposed Soskin's calculations of a large carbohydrate deficit with his own figures showing a deficit of only 27 Gm. of glucose,[20] and urged that there has been "overemphasis of the importance of an immediate restoration of glycogen stores in the liver."[25]

Since all authorities, including Joslin and Root, administer carbohydrate after the first four to six hours, the controversy is reduced to the question of whether the outcome is favorably influence by the early administration of dextrose and the maintenance of hyperglycemia.

The fatality rate was extremely low in the patients treated at the New England Deaconess Hospital under a regimen of withholding dextrose until the fourth to sixth hour of treatment. Because of the excellent educational program carried on by the Joslin group and the superior intelligence and economic status of their clientele, it might be expected that their patients would come under treatment relatively early in the

23. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, ed. 2, Baltimore, Williams & Wilkins Company, 1946, p. 1109.

24. Mirsky, I. A.: Franzblau, A. N.; Nelson, N., and Nelson, W. E.: The Role of Excessive Carbohydrate Intake in the Etiology of Diabetic Coma, J. Clin. Endocrinol. **1**:307, 1941. Footnote 2.

25. Root, H. F.: The Use of Glucose in the Treatment of Diabetic Coma, J. Clin. Endocrinol. **5**:353, 1945.

course of diabetic acidosis. On the other hand, a majority of the patients in our series had been unconscious for some time prior to their admission to the hospital. From these considerations it would appear that the condition of the patients reported on by Joslin and Root may not have been of a severity comparable to that of the patients admitted to city hospitals.

The close relationship of the condition on admission to the ultimate outcome makes a classification of initial severity a necessary preliminary to evaluation of any therapeutic regimen. Since in both Collen's series [13] and our own practically all patients with a severity index under 30 per cent recovered whereas almost all with a severity index over 60 per cent died, regardless of the type of therapy, it would appear that only cases in the intermediate group are suitable for the evaluation of a therapeutic regimen. Eighteen of the patients in the 30 to 60 per cent severity index range received dextrose early, while 7 received no dextrose during the first four to six hours. The condition of the patients in these two groups was of comparable severity (table 11), but the fatality rate was considerably higher in those receiving dextrose during the first four hours.

The results of this study show that the early administration of dextrose and the maintenance of hyperglycemia does not have a favorable effect on the outcome of diabetic coma. While the series is not large enough for statistical significance, the trend indicates that the early administration of dextrose exerts a deleterious effect.

Considerable emphasis has been placed on restoration of carbohydrate deficit and abolition of ketosis as primary goals in the treatment of diabetic coma. Soskin has demonstrated that hyperglycemia enhances carbohydrate utilization in depancreatized animals. Contrary to expectation,[26] we found that comparable doses of dextrose were retained more efficiently under much smaller doses of insulin when the blood sugar level was normal than when it was considerably elevated. In our cases the maintenance of hyperglycemia by early administration of dextrose appeared to reduce the efficiency of utilization of subsequent doses. Although Conn and Bauer [22e] attempted to demonstrate utilization of carbohydrate by patients with acidotic diabetes and hyperglycemia, their data support ours in that their 2 patients with blood sugar levels of over 400 mg. per hundred cubic centimeters on admission to the hospital retained only 8 and 30.7 per cent respectively of the dextrose administered during the first six hours of therapy. Poor retention of exogenous glucose in the presence of hyperglycemia is due in part to the limited capacity of the tubules to reabsorb glucose, a limitation which is

26. Drury, D. R., and Palmer, J. J.: Activity of Insulin in Diabetic Hyperglycemic Animals, Proc. Soc. Exper. Biol. & Med. **38**:394, 1938.

exaggerated in diabetic acidosis.[27] The prediction based on the work of Mirsky that early administration of dextrose and maintenance of hyperglycemia would hasten the abolition of ketosis was not borne out in our studies. Comparison of the saline and dextrose groups revealed no difference in the rate of disappearance of acetonuria.

Why should a procedure, which from the experimental work of Soskin and that of Mirsky appears to be physiologically sound, fail to accomplish its aims and even be harmful? The situation is clarified by consideration of the body as a whole. Hyperglycemia and ketosis constitute only one phase of the abnormalities in diabetic acidosis and are accompanied with striking alterations of electrolyte and water balance, with intracellular as well as extracellular dehydration and with severe disturbances of nervous, cardiovascular and renal function. Thus, the effect of any therapeutic regimen on these secondary disturbances is at least as important as its effect on the primary disturbances of carbohydrate and ketone metabolism. Soskin [28] has stated that physicians who do not administer liberal amounts of dextrose are like the chemist who forgets that the rate of a reaction is proportional to the concentration of the substrate. However, the purported beneficial effects of an excess glucose substrate on carbohydrate metabolism may be entirely nullified by unfavorable side effects. Our data show that these side effects are of considerable importance.

The following chain of events is set up by early administration of dextrose, which in all probability is damaging to the cells:

Glucose administration → hyperglycemia → excessive glycosuria → polyuria.

Polyuria would be expected to interfere with restoration of depleted body fluids and appeared to do so in Conn's patients. These patients received large amounts of dextrose in the first six hours and had diuresis equaling their intake. However, in our cases considerable retention of water and hemodilution occurred despite the polyuria. Hence, a further exploration of the deleterious effects of hyperglycemia and polyuria is needed. This is furnished through a comparison of water and chloride retention in our saline and dextrose groups.

A striking difference between the two groups in the handling of water and chloride became evident in the second period. The fluid intake of the dextrose group was only slightly larger than that of the saline group, but the output was nearly four times as great, largely because of an elevenfold difference in glucose output. As a consequence of the excessive glycosuria in the dextrose group, a greater proportion of the water intake than of the chloride intake was excreted. Hence, during the second period the dextrose group retained a fluid which was exceed-

27. Bjering, T., and Iverson, P.: Zuckerschwelle und Nierenfunktion, Acta med. Scandinav. **82**:193, 1934.

28. Soskin, S., in discussion on Root.[25]

ingly hypertonic in chloride content and probably hypertonic in sodium as well. The lack of an appreciable rise in plasma chloride content indicated a shift of intracellular water to the extracellular spaces, which thereby caused cellular dehydration. On the other hand, the saline group in the same period retained a hypotonic chloride solution without change in plasma chloride level, thus making water available to the cells. However, during the first period the saline as well as the dextrose group retained a hypertonic chloride solution. Much if not all of the surplus chloride could be accounted for by the rise in plasma chloride content. Thus the study of chloride balance failed to reveal definite evidence of increased cellular dehydration in either group during the first period. However, Sunderman's work [29] would suggest that a difference in distribution of water was present in the first as well as in the second of our experimental periods. He demonstrated in diabetic patients that hyperglycemia causes the withdrawal of water from the tissue and conversely that the return of the blood sugar level to normal causes the return of water to the tissues. Hence, the falling blood sugar level in the saline group probably allowed cellular hydration to occur despite the retention of chloride as a hypertonic solution. On the other hand, the maintained hyperglycemia of the dextrose-treated patients did not permit water to go to the cells and probably promoted cellular dehydration.

It should be emphasized that patients in poor clinical condition cannot dispose of even small amounts of dextrose, as evidenced by the rising blood sugar level. It is known that under hypoxic conditions in rats utilization of dextrose is impaired and its administration causes hyperglycemia.[30] Hyperglycemia may complicate shock and cardiac failure in human beings independent of diabetes mellitus. Elevation of the blood sugar level in cases of shock serves only to increase the cellular dehydration already present. In such cases administration of dextrose, even in small amounts, is not advisable.

SUMMARY

For 28 patients with severe diabetic acidosis or coma determinations of the blood sugar content, carbon dioxide–combining power, chloride and inorganic phosphorus contents and hematocrit readings were made at approximately four hour intervals for twenty-four hours. Quantitative urinalyses were made in parallel periods for glucose, chloride, phosphorus and nitrogen.

The intake was accurately recorded and was limited to water, sodium chloride, dextrose and insulin, supplemented in some cases by plasma,

29. Sunderman, F. W.: Water and Electrolyte Distribution in Diabetes Mellitus, Am. J. M. Sc. **205**:102, 1943.

30. Van Middlesworth, L.: Glucose Ingestion During Severe Anoxia, Am. J. Physiol. **146**:491, 1946.

blood or alkali. The cases were divided into three groups according to therapeutic regimen. The first, or "saline," group received no supplementary dextrose until the blood sugar level had fallen within the normal range. The second, or "dextrose," group received dextrose from the onset of therapy. The third group was treated similarly to the second during the first four hours but subsequently received sodium phosphate intravenously, the discussion of which forms the subject of another paper.

The administration of dextrose in the early hours of therapy resulted in prolonged hyperglycemia, pronounced glycosuria and polyuria. Diabetic patients in poor clinical condition could not tolerate even small amounts of dextrose without exhibiting a rise in the blood sugar level. The amount of exogenous glucose retained per unit of insulin was much greater at normal than at high blood sugar levels. The early administration of dextrose, by maintaining hyperglycemia, diminished the efficiency of utilization of subsequent doses.

Contrary to expectation, the early administration of dextrose or the maintenance of hyperglycemia did not accelerate the disappearance of acetone from the urine or the rise in plasma carbon dioxide–combining power.

Four patients in whom an uneventful course was anticipated from their status on admission to the hospital received dextrose in large amounts during the first few hours and went into shock within three to nine hours after the onset of therapy. The early administration of dextrose appeared to have an unfavorable influence on the clinical course in these patients and on the outcome in the group as a whole. For further evidence, the clinical analysis was extended to include a total of 55 consecutive cases of diabetic coma. Thirty-three of the patients in these cases were given dextrose during the first four hours, and the other 22 received no carbohydrate during this period. Although the condition in the two groups was of comparable severity on their admission to the hospital, as judged by the index of Collen, the fatality rate was considerably higher in the patients receiving dextrose during the first four hours than in those from whom it was withheld until the blood sugar level approached normal.

The maintenance of hyperglycemia appeared to be an indirect factor in the development of shock and in the poorer clinical results obtained when dextrose was administered in the first four hours. The secondary glycosuria and polyuria resulted in the retention of chloride as hypertonic solution and therefore probably caused an abstraction of intracellular fluid and further cellular dehydration.

The results of this study indicate that dextrose should not be administered in diabetic acidosis until the blood sugar level has fallen within or near normal range.

VENTRICULAR TACHYCARDIA AND BILATERAL AMAUROSIS PRODUCED BY QUININE POISONING

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CINCHONA derivatives are being used in increasing quantities by the medical profession. Quinine has particularly widespread use as an ecbolic and as an antimalarial agent. The related drug, quinidine, is gaining favor for the control of ectopic cardiac rhythms. Reports of toxicity following the overuse of quinine and its derivatives are abundant. There have been a few reports of amaurosis, with return of central vision, produced by toxic doses of quinine, and reports of the occurrence of ventricular tachycardia with overdosage of quinine have appeared in the literature; however, there is little information on the subject. The case presented here has unusual interest in that overdosage of quinine produced both ventricular tachycardia and bilateral amaurosis.

REPORT OF A CASE

J. M., a 45 year old white man, was admitted by police ambulance to Hines Veterans Administration Hospital on Dec. 29, 1946, in coma. No history was immediately available.

Physical Examination.—The patient was well developed, well nourished and slightly cyanotic. The rectal temperature was 98 F. The skin was cool and moist. The respiratory rate was 26 per minute, and respirations were shallow and rapid. He responded to painful stimulation with withdrawal movements of the extremities. There were a few old crusted excoriations about the scalp and face. The pulse was 140 and extremely feeble. Blood pressure tones were faintly perceptible—60 mm. of mercury systolic and 50 mm. diastolic. The pupils were dilated to 4 mm. in diameter, were round and equal bilaterally and did not react to light. On funduscopic examination, both disks were well outlined. The retinas were markedly pale, with maculas standing out as cherry red spots. The arterioles appeared attenuated,

From the Medical Service, Veterans Administration Hospital.

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and the veins were not engorged. The ratio of arteries to veins was 1 to 4. The arterial tree could be observed only up to 3 disk diameters from the optic disk margins. The neck vessels were somewhat engorged, and there was active resistance to hyperflexion of the neck. The chest was emphysematous, with a widened anterior-posterior diameter. The lungs were hyperresonant throughout. There were transmitted gurgles and throat sounds throughout both pulmonary fields, obscuring all other auscultatory findings. The borders of the heart could not be definitely determined, and no tones were audible. The abdomen was soft. The bladder was distended to just below the umbilicus. The edge of the liver was barely palpable below the right costal arch; the borders were firm and smooth. Rectal examination revealed the prostate to be of normal size. No masses were present. The brown fecal contents did not contain any blood. Deep tendon reflexes were present and equal bilaterally, as were the abdominal and cremasteric reflexes. No pathologic reflexes were elicited.

Laboratory Procedures.—A specimen of urine obtained with a catheter contained no albumin, sugar or acetone. The red blood cell count, the percentage of hemoglobin and the hematocrit reading were normal. The white blood cell count was 21,000, with a normal differential count. An emergency portable roentgenogram of the chest revealed pulmonary congestion. Emergency chemical examination of the blood revealed the blood sugar level, carbon dioxide-combining power and nonprotein nitrogen content to be within normal limits. A spinal puncture revealed clear fluid under normal pressure, a negative Pandy reaction and the presence of 4 cells per cubic millimeter. An electrocardiogram revealed the presence of ventricular tachycardia (fig. 1).

Course in the Hospital.—First day: The patient was immediately placed in an oxygen tent, and supportive measures were instituted. Three hours after his admission the electrocardiogram was available, and because of the presence of the ventricular tachycardia, a tentative diagnosis of probable myocardial infarction was made. A sister of the patient telephoned the hospital at this time and volunteered the following information: The patient was discharged from the Navy about one year previously and had since been working as a bartender. He was separated from his wife and had been living alone in a room. He had been ill since his release from the Navy with recurrent attacks of malaria. She further stated that she had on several occasions seen the patient swallow handfuls of quinine tablets, which he seemed to keep available.

Because of the possibility that the electrocardiographic abnormalities were produced by quinine poisoning, it was decided not to use quinidine for conversion of the abnormal rhythm. The patient was placed on papaverine hydrochloride, 0.065 Gm. intramuscularly every three hours. He remained in critical condition throughout the day. His pulse rate remained at about 130 per minute, and attempts to slow or alter the rate by stimulation of the carotid sinus or by eyeball pressure were unsuccessful, as expected.

Second Day: The patient's pulse rate was 88 and regular, and the blood pressure was 110 systolic and 80 diastolic. He responded but was extremely confused. His pupils remained dilated and fixed, and he was unable to distinguish light. An electrocardiogram revealed conversion to sinus rhythm and changes suggestive of early posterior coronary infarction (fig. 2).

Third Day: The patient became delirious and thrashed about wildly. He spoke of "bottles flying past and roaches swarming." He was placed on paraldehyde and chloral hydrate for sedations. An electrocardiogram revealed that the terminal segment changes had reverted to near normal (fig. 3).

Because of the rapid electrocardiographic recovery, a coronary occlusion now seemed highly improbable. At this time it was evident that the electrocardiographic changes and the eyeground findings could be attributed to quinine poisoning. An attempt to secure vasodilatation by the use of vasodilators was made. Nitroscleran (sodium nitrite) intravenously and nicotinic acid orally was used, in addition to papaverine hydrochloride hypodermically.

Subsequent Course: The patient became rational and quiet on the fifth day in the hospital. On frequent reexamination, no perception of light was evidenced bilaterally. Normal color gradually returned to the retinas, but the disks became pale and the arterioles became narrowed and could not even be observed in many places. A whitish perivascular bed remained, extending from the disks peripherally

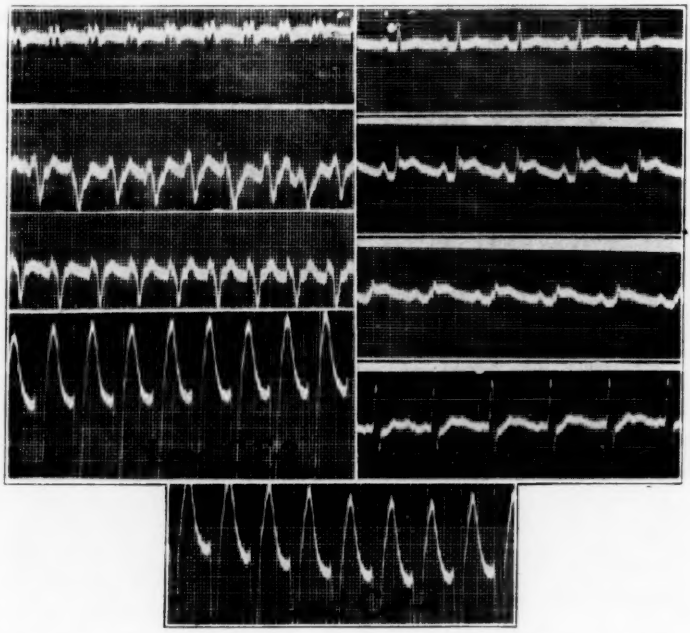

Fig. 1.—Electrocardiogram on Dec. 29, 1946, the date of the patient's admission, shows a regular tachycardia rate of approximately 140, with aberrant complexes, which was interpreted as indicating ventricular tachycardia. The tracing on the following day showed a normal sinus mechanism, with marked terminal segment changes in leads II, III and IV, which were interpreted as manifestations due to the injury currents resulting from basal infarction.

along the path of the attenuated, silver wire-appearing arteriolar trees. Six weeks after admission a central arterial blood column was present, extending peripherally one disk diameter from the optic disks. Return of light perception had then occurred. A short while later, counting of fingers at a distance of 18 inches (45 cm.) with both eyes was recorded. Light projection only could be obtained, but this was not entirely reliable. No further improvement was noted on subsequent examinations.

No history of involvement of the eighth nerve was elicited. The patient was able to hear a whispered voice 15 feet (4.5 M.) away with both ears. However, the audiogram revealed partial nerve deafness. There was normal hearing up to a frequency of 2,048 cycles per second and diminished hearing above this frequency, with a maximum of 70 per cent loss of hearing at a frequency of 6,000 cycles per second.

The electrocardiogram on Jan. 27, 1947, revealed no significant residual abnormalities (fig. 4).

Medical History.—When the patient had recovered from his acute symptoms, he gave the following information: No symptoms of illnesses of note antedated his military service. He was inducted on Aug. 7, 1942, and was discharged on Jan. 18, 1944, having served overseas in the Southwest Pacific from September 1942 to

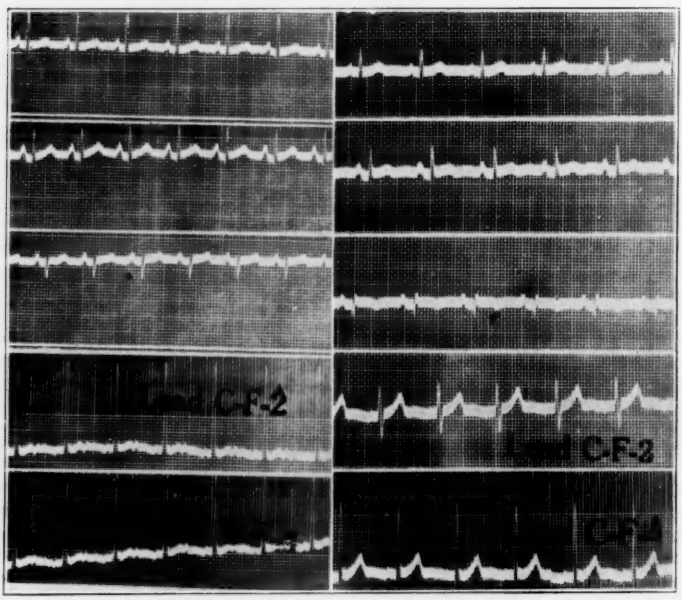

Fig. 2.—Electrocardiogram dated Jan. 1, 1947, two days later, shows a reversion of the standard leads to essentially normal configuration. Leads CF_2 and CF_4 show only notching of the T wave. The tracing on January 27 was interpreted as normal.

1943 in the Construction Battalion of the Seabees as a ship's fitter first class. The patient stated that he had four proved attacks of malaria while overseas, all treated in the sick bay with quinine. He also stated that on arrival in the States he had frequent recurrent attacks of malarial fever and was repeatedly hospitalized for the same, finally receiving a medical discharge.

Since his release from the Navy, he had been taking 15 grains (1.0 Gm.) of quinine daily. Despite this he continued to have episodes of chilly sensations occurring every fifteen to eighteen days, and, feeling that a recurrence of malaria was imminent, he would then take 45 grains (3 Gm.) of quinine daily until the

symptom disappeared. During this additional quinine therapy, he had a continuous "buzzing" in his ears. He further stated that he had been hospitalized on three occasions at Hines Veterans Hospital for treatment of malaria.

An investigation of hospital records revealed that on each of the three hospitalizations referred to the patient had given a history of having ingested large quantities of quinine immediately prior to each admission. During all three periods in the hospital, repeated smears did not reveal the presence of malaria, and the patient at no time had an elevation of temperature. A history of alcoholism was elicited at one time. All other studies were noncontributory.

History of Present Illness.—The patient stated that he had been entirely well until two days prior to his current admission to the hospital, when he felt feverish and because of this took 45 grains (3 Gm.) of quinine. He worked that day, but on the following day, because of malaise, he took at one dose the entire contents of a box containing 100 quinine tablets. He stated that these were almost all 2 grain (0.13 Gm.) tablets but that there were a few 5 grain (0.32 Gm.) tablets. He remembered falling to the floor shortly after this and recalled nothing further until his awakening at the hospital. He denied ingestion of any alcohol during the two days prior to this episode.

COMMENT

Quinine poisoning producing both amblyopia and ventricular tachycardia has not heretofore been reported. In most recorded cases of quinine toxicity resulting in amaurosis, symptoms of involvement of the eighth nerve usually preceded the symptoms in the eyes. In this case, however, no history of impairment of the eighth nerve was elicited, but audiometric examination later revealed partial eighth nerve deafness.

The action of quinine in the retina is reported as (1) being directly toxic to the ganglion cells and (2) operating on the retinal vessels to cause extreme vasoconstriction with resulting retinal ischemia and damage. In the vast majority of reported cases of amaurosis due to quinine poisoning the patients recovered much of their vision, with only a constricted field remaining. Duke-Elder [1] stated that in all cases the tendency is toward recovery; in the milder degree of poisoning the vision may recover in a few hours, but in more severe cases amaurosis may persist for several days or even weeks, and in this event some degree of atrophy of the nerve and some permanent loss of vision are invariable. Permanent blindness, however, has not been recorded. To all intents and purposes, the patient here reported on remained blind after the ingestion of a toxic dose of quinine.

On the whole, the cardiac manifestations of quinine poisoning have been noted infrequently. Schwartz and Jezer [2] showed that the intravenous administration of small doses of quinine dihydrochloride did

1. Duke-Elder, S. W.: Text Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1943, vol. 3, p. 3031.

2. Schwartz, S. P., and Jezer, A.: The Action of Quinine and Quinidine on Patients with Transient Ventricular Fibrillation, Am. Heart J. **9**:792-801 (Aug.) 1934.

result in transient periods of ventricular fibrillation in susceptible subjects. Sokolow [3] reported the occurrence of bundle branch block without other major manifestations of cinchonism following the ingestion of 10 Gm. of quinine in a 27 year old woman.

Williams and Ellis [4] pointed out the rarity of the incidence of ventricular tachycardia from all causes. In their report of 36 cases, organic heart disease was present in 35. The tachycardia was thought to be precipitated by administration of 60 to 100 grains (4.0 to 6.7 Gm.) of quinidine in 1 of the cases.

The effect of quinine on heart muscle is qualitatively similar to that of its isomer, quinidine. One of the major effects of quinidine on heart muscle has been accepted as that of slowing which is due to the action of the drug on the refractory period of the sinoauricular node, in which it decreases the rate of impulse formation. Large doses are said to cause cardiac arrest. However, Gold, Otto and Satchwell [5] showed that in addition to the prolongation of the QRS-T interval quinidine was also responsible for the production of sinus tachycardia. They also reported 7 instances of the precipitation of ventricular tachycardia or fibrillation after the use of quinidine in the treatment of paroxysms of auricular flutter and fibrillation.

The action of quinine on blood vessels in therapeutic dosage is that of vasodilation by direct action on the smooth muscle of the vessel wall. However, a toxic effect of quinine poisoning, that of retinal vasoconstriction, has been repeatedly reported and was observed in this case. The reported effect of the cinchona group on coronary vessels is that of vasodilatation. Kountz [6] did not observe any effect on coronary vessels with the use of 1 cc. of a 1 to 10 solution of quinidine in a heart-lung preparation of the revived human heart; however, Elek and Katz, [7] in experiments on isolated fibrillating dogs' hearts, reported that toxic doses of quinidine resulted in profound coronary dilatation of from 76 to 184 per cent lasting for six minutes.

The difficulty with which measurement of coronary blood flow is made is well known. Flow in isolated animal hearts can be measured

3. Sokolow, M.: Bundle Branch Block in Quinine Poisoning: Report of a Case, U. S. Nav. M. Bull. **45**:737-741 (Oct.) 1945.

4. Williams, C., and Ellis, L. B.: Ventricular Tachycardia: Analysis of Thirty-Six Cases, Arch. Int. Med. **71**:137-156 (Feb.) 1943.

5. Gold, H.; Otto, H. L., and Satchwell, H.: Use of Quinidine in Ambulatory Patients for Prevention of Paroxysms of Auricular Flutter and Fibrillation, with Especial Reference to Dosage and Effects on Intraventricular Conduction, Am. Heart J. **9**:219-237 (Dec.) 1933.

6. Kountz, W. B.: Studies on the Coronary Arteries of the Human Heart, J. Pharmacol. & Exper. Therap. **45**:65-75 (May) 1932.

7. Elek, S. R., and Katz, L. N.: Further Observations on the Action of Drugs on Coronary Vessel Caliber, J. Pharmacol. & Exper. Therap. **75**:178-182 (June) 1942.

with accuracy, but the applicability to the intact human heart is open to question. The following example will illustrate the unsettled nature of this problem. The effect of the vagus is usually accepted as being that of a coronary artery constrictor. Yet most workers report that acetylcholine injected intravenously into experimental isolated dogs' hearts causes vasodilatation. Katz and Jochim,[8] too, in their animal experiments, reported that the vagus acts as a coronary dilator.

The entire matter of vasomotor activity with reference to the coronary circulation and the mechanisms involved is not settled. There is little question that the episode of paroxysmal ventricular tachycardia in the case reported was due to the toxic effect of quinine. Whether the rhythm was initiated entirely by the direct effect of the drug on the myocardium or whether there was also an element of coronary artery constriction cannot be definitely stated. There was definite evidence that a severe degree of such vasoconstriction did occur in the retinal arteries. It seems entirely possible that vasospasm may have occurred in the coronary circulation. The experimental work previously cited does not justify such a presumption. However, these workers observed only transient effects lasting a few minutes. It seems possible that the toxic effect of quinine, producing retinal artery constriction, could similarly have caused coronary artery spasm. The electrocardiogram taken on the second day, showing a pattern indicating localized ischemia of the basal surface of the heart, further supports this possibility. The electrocardiographic pattern noted immediately after paroxysmal tachycardia usually indicates generalized myocardial ischemia due to temporary coronary insufficiency. If it is postulated that transient coronary spasm involving predominantly the basal coronary supply occurred, then localized ischemia of a degree which might give rise to electrocardiographic signs typical of the early stages of basal infarction might occur. The return of the electrocardiogram to normal was too rapid to justify a diagnosis of actual infarction. This reasoning does not justify the conclusion that coronary spasm occurred, however, since a latent sclerosis of the basal coronary vessels may have been present and the ischemia resulting from the tachycardia alone might well have been responsible for a localizing type of electrocardiographic pattern. Eisamen[9] has reported a case of ventricular tachycardia in which the electrocardiogram, after the cessation of the arrhythmia, resembled that in basal infarction. However, the return to normal was so rapid that a temporary ischemia rather than infarction seemed to be the logical explanation.

8. Katz, L. N., and Jochim, K.: Observations on the Innervation of the Coronary Vessels of the Dog, Am. J. Physiol. **126**:395-401 (June) 1939.

9. Eisamen, J. L.: Electrocardiogram Simulating Posterior Mycardial Infarction After Cessation of Paroxysmal Tachycardia, Am. Heart J. **30**:401-410 (Oct.) 1945.

Irrespective of the exact mechanism involved, the arrhythmia presented an interesting therapeutic situation. Ordinarily, the treatment would have been prompt administration of quinidine in an attempt to induce normal sinus rhythm. Only by fortuitous circumstances was the information concerning the prior ingestion of quinine received a few minutes before quinidine therapy would have been started. It seems likely that the use of quinidine in this patient might well have caused a fatal outcome.

SUMMARY

A case report is presented of a returned serviceman who resorted to the use of large quantities of quinine in the self care and prevention of alleged malarial fever. He was admitted in coma after the oral ingestion of at least 6 Gm. of quinine sulfate.

The overdosage of quinine produced a ventricular tachycardia, with rapid electrocardiographic recovery through a stage of marked myocardial ischemia simulating early basal myocardial infarction. A persistent bilateral amaurosis also resulted from this overdosage of quinine.

A theoretic discussion of the manner in which overdosage of quinine produced ventricular tachycardia is also presented.

RHEUMATOID ARTHRITIS IN CHILDREN

A Clinical Study

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KANSAS CITY, MO.

CHRONIC arthritis in children was first described not by Still but by Cornile [1] in 1864. In his classic thesis of 1897 Still [2] drew attention to the fact that in a series of 22 cases of chronic arthritis in children the disease occurred in 12 before the second dentition and was accompanied with changes in the viscera, generalized glandular adenopathy and multiple signs of systemic reaction. It is usually asserted that Still's disease is the less commonly occurring childhood manifestation of that disease or group of diseases which in adults is described as rheumatoid or atrophic arthritis. Still's observations have been confirmed by many observers, including Gibney [3] in 1912, Johannsen [4] in 1923 and Genthon in 1937.[5] Assuming for the present that Still's disease and juvenile rheumatoid arthritis are synonymous terms, one is struck by the failure of these contributors to convey more than an incomplete survey of the clinical aspects of the disease. Influenced by the material at hand, they have inculcated in the minds of physicians a concept of a rare, unusually crippling condition, static in course and largely intractable to therapy. In 1937 Colver,[6] at the Great Ormand Street Hospital in London, made a follow-up study of all patients hospitalized with this disease after the first World War. When examining these older patients, he was "impressed by the frequency of complete recovery and by the relative infrequency of joint crippling." This was the first rational challenge to the melancholy viewpoint of the older clinicians.

Beginning in 1941, I was given an opportunity to treat 10 children suffering from this disease.[7] After a five year observation period, it

Dr. Richard Freyberg contributed valued assistance in the preparation of this manuscript.

1. Cornile, A.: M. Soc. d. biol. **1**:3, 1864.
2. Still, F. F.: Tr. M. Soc. London **130**:47, 1817.
3. Gibney, V. P.: M. Rec. **82**:93, 1912.
4. Johannsen, N.: Acta pædiat. **2**:354, 1923.
5. Genthon, M. J.: Thesis, Paris, no. 810, 1937.
6. Colver, T.: Arch. Dis. Childhood **12**:253, 1937.
7. By Dickson & Diveley Clinic, Kansas City, Mo., through the courtesy of Dr. Frank Dickson.

seemed advisable, in the light of a clinical experience which did not entirely follow that described in the literature, to review the work of other clinicians in this field.

By definition, the disease in the group of 10 cases mentioned previously and in all cases in the material taken for study fell into the category of chronic disease of the joints of children prior to puberty, nonspecific in cause, systemic in nature and characterized by persistent changes in the synovia, which in some cases but not invariably led to changes in the cartilage, ligaments and muscles of the joint involved.

Within these limits, the entire recorded clinical experience of the New York Hospital, the Hospital for Special Surgery and the New York Orthopedic Hospital was reviewed.[8] Furthermore, for a period of six months I was granted the privilege of personally examining and following all children presenting nontraumatic effusion of the joint in the outpatient department of the Hospital for Special Surgery. To the 10 cases previously mentioned 25 cases were added from these records on a basis of having been followed by reliable observers over a continuous period of three years or more. All tabulation herein noted refers to these 35 cases.

INCIDENCE

Coss and Boots[9] have reported the incidence of chronic arthritis in children under 12 to be 4.9 per cent of the total incidence of all rheumatoid arthritis seen in their clinic. Kuhns and Swaim[10] have reported 13 cases in a series of 314 hospitalized patients (4.17 per cent). On the other hand, it is impossible to estimate accurately the incidence of the disease in the child population. That there is reason to believe that the incidence is greater than records would indicate is supported by the fact that 3 cases were recognized in the six months study period at the Hospital for Special Surgery. In normal circumstances the disease in these cases would not have been classified as rheumatoid arthritis and yet it fell within the limits of the aforementioned definition. During this period, no patients with obvious signs of the disease were admitted to the hospital. In the present series there was no indication that age or sex (21 girls, 14 boys) was a significant factor in the incidence of the disease.

PRECIPITATING FACTORS

A. *Infection.*—In this series of cases the relationship of bacterial invasion to the presence of the disease was studied by culture of material obtained from joints as well as by culture of swabs taken from other

8. The reviews were made possible through the courtesy of Dr. Samuel Levine, Dr. Philip Wilson and Dr. Alan DeForest Smith, respectively.

9. Coss, J. A., Jr., and Boots, R. H.: To be published.

10. Kuhns, J. G., and Swaim, L. T.: Disturbances of Growth in Chronic Arthritis in Children, Am. J. Dis. Child. **43**:1118 (May, pt. 1) 1932.

parts of the body, notably the upper respiratory passages. In no instance did a culture of fluid from the joints yield pathogenic organisms. On the other hand, all patients admitted to the New York Hospital had cultures taken from the nose or throat and in virtually each instance pathogenic organisms (hemolytic Staphylococcus aureus and alpha and beta hemolytic streptococci) were demonstrated. The significance of such a finding is subject to question. Records of 20 diabetic children admitted to the same institution showed an almost equally high incidence of pathogenic organisms in the upper respiratory passages. In these circumstances there is the temptation to dismiss infection as an etiologic factor in juvenile rheumatoid arthritis, and yet in 16 of 35 children (45.7 per cent) the incidence of respiratory infection was the outstanding event in the history of the onset of disease. The following is an illustrative case.

In B. L., a previously well 10 year old girl, an acute infection of the upper respiratory tract developed, characterized by sore throat, nasal discharge, cough and elevation of temperature. The child was bedfast for three weeks during the acute stage of the illness. At the end of this time partial activity was allowed. In the fourth week of convalescence migratory polyarthralgia developed, and on admission to the hospital two months after the onset of her illness the child showed typical manifestation of rheumatoid arthritis in the hands and knees.

Hence, the question arises as to whether the presence of pathogenic organisms is more significant in the throats of children who suffer or will suffer from rheumatoid arthritis than in children who are not subject to rheumatoid arthritis or whether, to paraphrase Rich,[11] speaking of rheumatic fever, "the lesions of [rheumatoid arthritis] may be due not to direct action of a bacterial toxin, but may represent the effect of a hypersensitive reaction to bacterial products." Studies on the immune reactions of children suffering from rheumatoid arthritis have been reported by Boots and Coss in a series of 56 cases. Coss[12] may be quoted as follows: "The streptococcus agglutination reaction in children, taken repeatedly over a period of fourteen years, was negative in 32 of 35 cases. [The three positive reactions were subject to question.] It is our impression that positive agglutination is rare in children." Antistreptolysin titers were done in 24 cases, and, "the high median of two hundred and fifty obtained was considered to be definitely above normal,[13] considering titers up to one hundred as normal, titers of one hundred to two hundred as suggestive of recent streptococcic infection and titers of over two hundred as being almost certain evidence of recent streptococcic infection."

With respect to the 16 cases in which a positive history of preceding infection was obtained, analysis showed certain common pathologic

11. Rich, A. R., and Gregory, J. E.: Bull. Johns Hopkins Hosp. **73**:239, 1943.
12. Coss, J. A., Jr.: Personal communication to the author.
13. Coss and Boots do not indicate how many of the 24 patients had high titers.

features: (1) the infection tended to be mild; (2) there was a lag period of three to ten weeks between the onset of the infection and the development of symptoms in the joints and (3) symptoms in the joints persisted for months or years following the subsidence or the disappearance of the original infection.

These findings should be contrasted with the sequence of events which is obtained when the general reaction to infection, as characterized by leukocytosis, elevation of body temperature and radial pulse rate, may be said to follow a "normal" pattern, which the following case illustrates.

J. S., a 6 year old boy, was chilled by exposure to low temperature. His shoes and feet were soaked. Three days later, pain developed in the knees, and he limped. The following day he was unable to put on his shoes because of swelling in the feet. On his admission to the hospital he complained of feeling tired and achy. His temperature on admission was 102 F., the pulse was 130 beats per minute and the respirations 24 per minute. His cheeks were bright and flushed, and the skin was hot and dry. There was a hot tender mass under the angle of the jaw on the right. The examiner noted swelling, redness and tenderness of the small joints of the hands and the feet. The total white blood cell count was 16,000. The erythrocyte sedimentation rate was 27 per minute. (Blood culture was not taken.) The child was treated by application of heat to the mass, and he was given rest and salicylates. Symptoms in the joints disappeared in twenty-four hours. The temperature and erythrocyte sedimentation rate were normal on the second day.

This child has been followed for three years and has shown no evidence of cardiac disease or disease in the joints. The characteristics of this type of clinical course are as follows: (1) the illness is acute; (2) the immune response to the illness is prompt, and (3) the development and the subsidence of abnormality in the joints corresponds chronologically to the cycle of disease in the whole body.

B. *Trauma.*—A definite history of trauma preceding the onset of disease in the joints was obtained in 7 cases, or 20 per cent. It is recognized that traumatic injury of the joints will result in a definite sequence of events in all children, that is to say, a blow in the area of a joint sufficient to cause contusion of the synovia, hemorrhage and exudation into the joint will be followed by effusion, muscle spasm and limitation of motion. The more than casual significance of trauma as a precipitating factor in rheumatoid arthritis in children may be seriously considered in those instances in which (1) the persistence of abnormality of the joints following injury is much longer than might reasonably be expected from the nature of the injury; (2) the severity of the reaction of the joint to trauma is far out of proportion to the severity of the injury or (3) pathologic features develop in joints other than those directly traumatized. The following case is illustrative.

M. M., a 6 year old boy, was brought to the hospital complaining of pain and swelling of the knees. He stated that he had been kicked in the knee one month

previously. No immediate pain or disability followed the blow, but one week later swelling, flexion deformity and mild limp developed, which persisted up to the time of his admission to the hospital, when clinical examination confirmed by roentgenologic findings showed swelling in both knees.

C. *Allergy.*—There were 2 instances of rheumatoid arthritis in children in whom allergic reactions were associated with the onset of disease. The following is an illustrative case.

TABLE 1.—*Clinical Evolution of Juvenile Rheumatoid Arthritis*

Phase	Duration	General Clinical Characteristics	Local Clinical Characteristics	Comment
Prodromal	Several days to several weeks	Severe systemic reaction; fever, malaise, tachycardia and nosebleed	Migrating transitory polyarthritis more or less indistinguishable from rheumatic fever	Occurred in 6 of 29 New York Hospital cases
Period of extreme activity of rheumatoid process	Three months arbitrarily is the minimal time of continuous activity of primary arthritic process. Six years was the longest observed time of continuous activity of the primary arthritic process in any of these cases; it might last longer	Slight elevation of temperature; cachexia; usually presents wasting, loss of appetite, failure to gain weight; elevation of sedimentation rate	Active inflammatory reaction in joints; effusions, tenderness to palpation, warmth and muscle spasm. Redness is rare except in infants or when allergic factors are present. Pain at rest is usually absent in early months. Changes in the joints are sullen and persistent *	
Period of stabilization of rheumatoid process	Approximately 6 months †	Little or no systemic reaction; patient apparently well; sedimentation rate usually continues to be elevated; patient has no subjective complaint but remains underweight	No new joints are involved, but excess activity may provoke exacerbation; effusion without pain may persist	This is an entirely arbitrary assumption, but it is important clinically since during this period joint mobilization must be carefully watched for evidence of exacerbation
Quiescence	All subsequent time	Normal health	Complete recovery or residual joint defect, influenced further only by resultant wear and tear	If joint disease occurs at this time, it is spoken of not as exacerbation but as recrudescence

* Any joint in the body may be involved in the prodromal phase, while in the active phase the ankles, knees, hands, wrists and occasionally the elbows are involved. Synovial and cartilage involvement of the temporomandibular joints, the cervical region of the spine, the hips and the shoulders is rare in the active phase and indicates a bad prognosis.

† In 2 incompletely observed cases painless persistent effusion lasted five years in children otherwise apparently well.

L. P., a 7 year old girl, began to have attacks of difficult respiration and swelling of the face, which occurred at forty-eight hour intervals and lasted about twenty-four hours. When these attacks had persisted for several weeks she was found to react positively to most of the commonly inhaled and ingested antigens. She lost weight, and after the first month attacks were accompanied with diffuse pains in the joints. Four months following the onset of the attacks there developed persistent changes in the joints.

COURSE AND CHARACTER OF THE DISEASE PROCESS

Consideration of a large number of cases of juvenile rheumatoid arthritis has suggested the use of certain terms to describe the chronologic cycle of the disease and to estimate its varying degrees of severity. While these terms are arbitrary, they are also purposeful inasmuch as they further clinical appraisal and aid in the adoption of rational management.

In respect to time, the cycle has been divided into four phases: prodromal, period of extreme activity, period of stabilization and period of terminal quiescence. Table 1 is a generalization of the clinical evolution of juvenile rheumatoid arthritis from its prodromal phase to its final subsidence.

In respect to severity, the disease may be classified as mild, moderate or severe, depending on the duration of the process, the degree of involvement of the joints and the nature of the constitutional reaction together with the presence of associated visceral lesions (table 2). Of 35 cases reviewed, in 11 the disease was classified as mild, in 19 as moderate and in 5 as severe. The cases of severe disease corresponded in most respects to those described by Still. The incidence of only 11 cases out of a total of 35 in which the disease was mild does not represent an accurate estimate of the relative frequency of the mild form. This is discussed in the section on incidence.

Recrudescence.—When children suffering from rheumatoid arthritis have been followed over a long period (five to fifteen years), a majority have been observed to reach a clinical state which has been described as "terminal quiescence." This is in agreement with the statement of Colver to the effect that the disease is a self-limited process. However, it was Colver's opinion that in all cases the disease became quiescent after at the most seven years and that in no case was there "recrudescence" after a quiescent period of eighteen months. This was not the experience of the patients studied, 28 of whom were observed for more than five years. Of these 28, 9 experienced a second attack of rheumatoid arthritis after periods of terminal quiescence ranging from two to eight years. In the 9 cases in which recrudescence was observed the causes appeared to be (*a*) infection (5 cases), (*b*) trauma (1 case), (*c*) exposure (1 case), (*d*) no known cause (2 cases).

In 1 instance recrudescence occurred in a boy at approximately the time of puberty and resulted in a different type of disease than that from which he had been suffering originally. This case will be described later. A second relapse occurred in a girl aged 16 years in whom the original childhood disease was experienced at the age of 6 years and reached terminal quiescence when she was 8. These cases are of extreme importance, for they indicate that puberty does not confer immunity to future disease in a person who has had an initial attack

in childhood and that puberty is not a satisfactory end point in time for final evaluation of the end results of rheumatoid arthritis in a child.

There does seem to be some indication that infections which may have been the precipitating factors in the original attacks are better tolerated at a later time when quiescence has been established. For example, the girl mentioned previously suffered scarlet fever at the age of 12 without recrudescence of rheumatoid arthritis.

In every instance the damaging effect of the recrudescent disease on the locomotor system has been more severe than that of the original attack.

TABLE 2.—*Severity of Rheumatoid Arthritis in Thirty-Five Cases Studied*

	Duration of Disease Process	Type of Joint Involvement	Constitutional Reaction	Associated Visceral Lesions	Residual Joint Effects	Comment
Mild	3 to 12 months	Mild synovial effusion and thickening of one knee or several small joints of the hands	Mild or absent	None	None	In a period of 6 months 3 cases were recognized at the Hospital for Special Surgery, while no case of moderate or severe degree was observed during this time
Moderate	2 to 3 years	Marked synovial effusion and thickening of the joints of the hands, knees, feet and occasionally elbows and ankles; minimal changes in the joint cartilage	Moderate loss of weight, loss of appetite, increased nervous irritability and elevation of the daily temperature 1 to 3 degrees F. in the first 6 months; elevation of sedimentation rate	None	Varies from no residual effects to moderate crippling	
Severe	6 years	Progressive destructive changes, involving many joints, including those of the cervical region of the spine, the temperomandibular joint and the shoulders	Severe cachexia; intermittent acute elevation of the temperature as high as 103 or 104 F.; high sedimentation rate	Nonspecific visceral lesions occur in about half of all cases labeled severe	Extreme deformity	The characteristic clinical feature of the severe type of disease is an inexorable and unremittingly progressive course, with little evidence of remission at any time

PATHOLOGIC PROCESSES

Joints.—During the active stage of the disease six knees were subjected to exploration for reasons of diagnosis or treatment. The lining of the joint was found to be thickly hyperemic and edematous. Microscopic sections showed focal collection of lymphocytes and increased tissue vascularity in folds of endothelium-lined synovia (villous synovitis). There was moderate formation of pannus in 2 cases. In 1 case the lateral femoral condyle was flattened, although the articular cartilage was not eroded. These findings suggest that while the lesions

in the synovia of the knees of children with rheumatoid arthritis resemble in every way those in adults, pannus formation is more limited and destruction of cartilage less severe. It is possible that there may be some correlation between the late or minimal destruction of the joint cartilage and the clinical absence of hypertrophic changes in the knees of the children studied. Table 3 summarizes the distribution of involvement of the joints in 35 cases of rheumatoid arthritis in children. In referring to this table it is to be noted that the prognosis as to function varied according to the joint involved; for example, the function of the knees was generally well restored, the elbows almost invariably lost motion but were infrequently ankylosed, involvement of the carpal joints frequently led to coalescence and the prognosis in involvement of the wrists was relatively poor. Involvement of the ankle joints

TABLE 3.—*Involvement of the Joints in Thirty-Five Cases of Rheumatoid Arthritis in Children*

	Occurrence *	Deformities During Active Stage *	Total Residual Joint Defects *	Ankylosis *
Knees	33	Approximately 50%	8	3
Elbows	15	15	14	1
Hands (metacarpals, phalangeal, interphalangeal, carpal)	32	Not specified	11	Not specified
Wrist	9	9	4	1
Tarsal	Not specified	Not specified	..	2
Ankle	9	9	..	2
Temporomandibular	6	6	5	..
Cervical region of the spine	7	7	5	5
Shoulders	2	2	2	2
Hips	2	2	2	1

* Figures refer to individual joints and not to cases.

rarely led to permanent joint disturbance, and when this did occur, ankylosis was the rule. There was no instance of involvement of the dorsal or lumbar regions of the spine and no instance of involvement of the sacroiliac joints. It would seem that rheumatoid spondylitis (Marie Strümpell) does not occur in children. However, 1 of the patients studied experienced recrudescence at puberty, and in contrast to the childhood type of disease the recrudescence was characteristic of Marie Strümpell spondylitis.

J. L. (present age, 20 years) experienced the onset of rheumatoid arthritis at the age of 6, with initial involvement of one ankle and later involvement of both hands. He was free from disease of the joints from age 8 to age 15 except for one brief instance of effusion in the ankles which followed an acute respiratory infection. At the age of 15 effusion of the knees developed, and at 16 backache was first noted. Roentgenograms of the sacroiliac joints at the age of 17 demonstrated ankylosis.

Typical hypertrophic changes accompanying static defects were observed only in the feet. (These included splaying of the anterior arch

of the foot, hallux valgus, tailor's bunions, claw toes and overlapping toes.)

It should be stated here that the tendency in healed joints was toward increased laxity in the capsules. In the fingers in particular it was noted that deformity tended to be due to laxity of the joints and to intrinsic muscle attrition rather than to defect in the joints. A search for a consistent mode of joint progression in the cases under investigation was fruitless.

Bones.—There is a local disturbance of the calcium content of the bones adjacent to involved joints even in mild forms of juvenile rheumatoid arthritis. Whether this is due to alteration of the balance between absorption and deposition of calcium or to atrophic changes in the matrix has not been established. It should be observed, however, that no changes in the relative constituents of the serum have been consistently observed, and, what is more significant, the process of decalcification cannot be ascribed to disuse, since a return to normal function does not result in restitution of normal calcium content in the bones. Observations as late as ten years following recovery have in no instance demonstrated normal calcium content. The absence of restitution indicates a basic disturbance in the process of calcium deposition in the bones, the nature of which is not known, but which may be fundamental to the occurrence of the disease. The demineralization of the epiphyses may result in increased fragility of these structures. Crumbling and early fusion may ensue in cases of severe disease, with corresponding disturbances of growth. The subject of disturbance of growth in rheumatoid arthritis in children has been exhaustively reviewed by Kuhns and Swaim,[10] who have reported 4 instances in a series of 13 cases.

Muscles.—No special studies of histologic changes in the muscles were made in the series of cases under investigation. The work of Steiner, Freund and others[14] has shown that in adult rheumatoid arthritis morbid changes consisting of focal collections of monocytes and lymphocytes together with perineural cell infiltration may be consistently found. Freund[15] made postmortem studies of the muscles of 2 children suffering from this disease and found changes in the muscles in no way differing from those in the muscles of adults.

Viscera.—Still,[2] Chauffard[16] and Felty[17] have drawn attention to the incidence in rheumatoid arthritis of lesions in organs other than

14. Steiner, G.; Freund, H. A.; Leichtentritt, B., and Maun, M. E.: Am. J. Path. **22**:103, 1946.

15. Freund, H. A.: Personal communication to the author.

16. Chauffard, A., and Ramond, F.: Rev. de méd., Paris **16**:345, 1896.

17. Felty, A. R.: Bull. Johns Hopkins Hosp. **35**:16, 1924.

joints. Reporting recent postmortem studies, Rosenberg,[18] Bennett,[19] Bayles [20] and Portis [21] have discussed the question as to whether such lesions represent an integral part of rheumatoid arthritis, whether they represent a series of lesions developing from a common etiologic factor or whether they are an entirely distinct coexisting disease. Rosenberg and his co-workers reported autopsies on 30 subjects who had had rheumatoid arthritis; fatal cardiac lesions were found in 10, and cardiac lesions indistinguishable from those of rheumatic fever were found in 16. This contrasts with the unreported random incidence of approximately 5 to 10 per cent of lesions considered to be characteristic of rheumatic fever in serial autopsies at the New York Hospital. It indicates that perhaps cardiac lesions occur more frequently in subjects with rheumatoid arthritis. Likewise, the high incidence of amyloidosis in rheumatoid arthritis is just beginning to be appreciated. Portis has reported 7 instances in 14 autopsies on children. It is well known that amyloidosis can be produced experimentally by repeated injections of sodium caseinate. In the German literature there are reports of amyloidosis in laboratory animals used to produce antiserums, particularly streptococcus antiserums. Moschowitz [22] postulates that amyloidosis is not caused by arthritis but that the two are reactions to the same injury. Lesions of the eye, the spleen and lymphatic system, the liver, the kidneys and the colon have been discussed in the literature.

Two patients in the series of 35 studied showed positive evidence of cardiac disease during life. The assumption that cardiac disease was present was based on the observation of gross enlargement of the heart by physical and roentgenologic examination, on the presence of harsh systolic murmurs, heard loudest at the base, and on the elevation of the apical pulse rate at rest to 140 beats per minute. Both children were hospitalized for the entire duration of their illness.

Case 1.—E. W. died at the age of 13 at St. Luke's Hospital, Kansas City, after four years of continuous hospitalization. Cardiac disease appeared in the third year of hospitalization and coincided with the development of severe destructive changes in the joints. Clinically, death was ascribed to congestive heart failure. At autopsy extreme enlargement of the liver and mild enlargement of the spleen were encountered. A sterile seropurulent exudation was present in the pericardial sac. There was thickening and retraction of the aortic valves. Senile atheromatous lesions were present in the walls of the aorta. Microscopic examination of the tissues showed chronic passive congestion of the liver and spleen, with necrosis

18. Rosenberg, E. F.; Baggenstoss, A. H., and Hench, P. S.: Ann. Int. Med. **20**:903, 1944.

19. Bennett, G. A.: Ann. Int. Med. **19**:111 (July) 1943.

20. Bayles, T. B.: Am. J. M. Sc. **205**:42, 1943.

21. Portis, R. B.: Pathology of Chronic Arthritis of Children (Still's Disease), Am. J. Dis. Child. **55**:1000 (May) 1938.

22. Moschowitz, E.: Ann. Int. Med. **10**:73, 1931.

of the central veins of the liver. Numerous areas of perivascular infiltration and one fresh vegetative lesion were found in the auricular myocardium.

CASE 2.—L. M., a 14 year old boy, has been hospitalized for nine years at St. Luke's Hospital, Kansas City. Clinical evidence of cardiac disease appeared in the eighth year of hospitalization and occurred in a period of recrudescence of disease of the joints which followed an infection of the middle ear.

In a third case autopsy was not performed, and although clinical evidence during the patient's life suggested the presence of cardiac disease, it was not sufficiently definite to support a positive diagnosis. In the records of 6 cases at the New York Hospital suspicion of cardiac disease was entertained by the attending clinicians. Dr. Harold Stewart of that institution kindly reviewed the 6 cases, and with the exception of 1 in which the possibility of rheumatic fever was not ruled out he expressed doubt as to the presence of cardiac disease in the group. In no case did the electrocardiogram show significant alteration in the conduction of the nerve impulse through the heart muscle.

One case of iritis was observed. The original ocular involvement occurred simultaneously with original lesions in the joints and impairment of vision followed. The patient had a relapse twelve years later, and acute iritis developed again in the same eye, with further reduction in vision. Four years following relapse, the disease in both the iris and the joints was completely quiescent.

In 5 of the 35 cases there was unequivocal clinical evidence of enlargement of the spleen; in 1 of these there was generalized lymphadenopathy. In 6 cases hepatomegaly was present. In these cases there was no evidence, by physical examination or laboratory study, of any factor directly responsible for the condition other than the presence of chronic passive congestion or of amyloidosis in certain fatal cases. There has been no agreement as to the significance of generalized lymphadenopathy in rheumatoid arthritis in children. To Still it was an essential feature of the disease. Colver stated that in his series of cases the aforementioned findings were commoner in patients in whom the disease began in the first four years of life. According to Colver, the presence of hepatomegaly or splenomegalia was of no prognostic significance in these cases.

It should be emphasized that with 1 exception there was clinical evidence of visceral lesions only in certain of the cases of severe disease. There was no evidence of such involvement in any of the cases of mild disease.

Psychologic Phenomena.—In addition to organic pathologic changes, there should be mention of the definite occurrence of psychic disturbance in about one third of the cases. In 7 out of 20 cases at the New York Hospital, where careful histories were obtained, there was a record of change in personality incidental to development of the dis-

ease. The changes consisted in aberrations of mood and personality, fear complexes and hyperirritability, which were not characteristic of the child prior to the onset of the disease and which disappeared when the child regained normal health. Two children were subjected to extensive psychometric examination and were adjudged to be of low intelligence level. I was able to examine 1 of these patients eight years after her acute illness. She at present holds a steady though menial job in the hospital and is considered to be a good worker. She has progressed through three forms of high school. The second patient was recently passed by Selective Service. One of the patients in the present series made two suicidal attempts. At present, three years later, he is a fairly stable person.

DIAGNOSIS

Diagnosis in this disease is frequently erroneous. It is seldom established in the early stages. The four mistakes commonly made are as follows:

1. The mild attack may be passed over entirely as a minor traumatic incident or labeled under such descriptive terms as toxic, nonspecific or villous synovitis.

2. Rheumatoid arthritis in children frequently exists as a monarticular disease, and in overlooking this clinicians tend to misdiagnose the disease, calling it tuberculosis.

3. It is frequently impossible in one examination to distinguish between rheumatoid arthritis and rheumatic fever.

4. In the absence of definite substantiating evidence there is a tendency to dismiss the cases as instances of brucellosis, syphilis or gonorrhea.

The outstanding diagnostic error in the management of rheumatoid arthritis consists in the confusion of the monarticular form with tuberculosis. This error was made no less than seven times in the 35 cases studied. Two patients were subjected to surgical treatment in these circumstances. Monarticular onset occurred in 15 patients, usually in the knees. Extension to other joints was the rule in these patients, but there was not infrequently a lag of two to four years before other joints became involved. Unfortunately the synovitis of tuberculosis may closely resemble that of rheumatoid arthritis, and in cases in which tuberculosis is actually present in the joint the biopsy specimen may not contain bacilli or tubercles. Significant demineralization of the epiphysis may result in marginal pitting or erosion, which is indistinguishable by roentgenologic examination from that of tuberculosis. Analysis of aspirated fluid from the joint is not helpful, since the cell count and the chemical constituents of the fluid may be altered in the same manner and degree in the two types of disease. If tuber-

culins are administered in 1 to 100 concentration and the reactions are negative, it may be assumed that tuberculosis does not exist. Confusion arises when the reaction to tuberculin in average concentration is positive and when biopsy does not reveal the disease. In these instances there can be no answer to the diagnostic problem save that derived from serial observation over an extended period. It will then be observed that the tuberculous joint goes through a longer chronologic phase of morbid development, that quiescence of the pathologic process requires a longer period and that reactivation follows more closely on active use of the extremity. The appearance of a second involved joint may be said virtually to settle the issue in favor of rheumatoid arthritis. In the absence of positive diagnostic evidence, physicians should be cautious in proceeding to the fusion of a joint for tuberculosis.

The differentiation between two such closely related diseases as rheumatic fever and rheumatoid arthritis has not always been possible because in some cases of rheumatic fever symptoms in the joints have for a time overshadowed evidence of cardiac disease and have persisted for as long as six months. That cardiac lesions of major severity do occur in rheumatoid arthritis has already been demonstrated, and it has not been shown that the two diseases may not occur simultaneously. The diagnostic difficulty may be represented by the following case.

R. H., an 8 year old boy, complained for two years of aching in the knees and thighs. Pain was transient and not associated with fever or changes in the joints. A short systolic murmur was detected. It was heard best at the third and fourth interspaces close to the sternum. Three weeks previous to his admission to the hospital an infection of the upper respiratory tract developed, followed by a low grade elevation of temperature and fleeting pains in the wrists, fingers, knees and ankles. Examination on admission demonstrated the systolic murmur without cardiac enlargement. The blood pressure was 133 systolic and 90 diastolic and the pulse rate 80. The abdomen was normal. Consultation with arthritis service resulted in recording of the opinion that the fusiform swelling of the fingers was typical of rheumatoid arthritis. The sedimentation rate was normal, as was the blood cell count. Fluoroscopic examination of the chest and an electrocardiogram showed no evidence of cardiac abnormality. During his stay in the hospital the patient had an elevation of body temperature to 102 F. daily. He was given adequate dosage of salicylates, without appreciable effect on the disease. There was loss of weight. Three weeks after his admission erythema multiforme developed and repeated electrocardiograms showed first stage block. Three months later a typical presystolic mitral murmur developed, and eight months after the onset of disease limitation of motion and thickening of metacarpophalangeal joints was described by the attending clinician.

Study of such cases indicates that sooner or later cardiac disease becomes manifest in rheumatic fever while symptoms in the joints will obviously eventually dominate the picture of rheumatoid arthritis. During the prodromal state, the two diseases may be identical. It should be observed that the joint effusion present in rheumatic fever is

transient, lasting only a few days. This is followed by a brief period of stiffness and sometimes itching. The redness of the joint seen in rheumatic fever is rarely observed in rheumatoid arthritis. Clinical experience supports the assertion that a child suffering from rheumatic fever will frequently exhibit elevation of body temperature without appearing to be notably sick, whereas the child with fever in rheumatoid arthritis is obviously extremely ill.

Diagnosis in the mild form of rheumatoid arthritis must rest positively on the persistence of effusion in the joints and negatively on the exclusion of other diagnostic possibilities. It must be appreciated, for example, that mechanical factors such as prolonged immobilization of an extremity in plaster may be followed by mild swelling of the joints. Heavy children with retarded epiphysial centers frequently complain of aching in the joints in the weight-bearing extremities. On the negative side, there is no available evidence to suggest either that such conditions as brucellosis actually produce objective changes in joints or that syphilitic or gonorrheal arthritis in children is a reasonable diagnostic possibility. This question was pursued in the record libraries of the three hospitals previously mentioned, in addition to which access was had to the records of the Bellevue Hospital, New York.[23] At the Hospital for Special Surgery there is record of a Charcot joint (hip) occurring in a boy of 15 years. This is the youngest patient in whom syphilis of the joint was demonstrated. Study was made of all children at the aforementioned hospitals in whom a diagnosis of gonorrhea was made. Although gonorrheal vaginitis and gonorrheal conjunctivitis are not uncommon, there were no proved cases of gonorrheal arthritis. In 1 instance, in which gram-negative diplococci considered to be characteristic of gonorrhea were cultured in a smear from the urethra of an 8 year old girl admitted to Bellevue Hospital, there was coexistence of acute arthritis of the elbow. This inflammatory process in the joint subsided after two weeks. There was no aspiration and no follow-up.

TREATMENT

The conditions under which this material has been gathered make it impossible to compare results obtained from different means of treatment or to evaluate any single therapeutic approach; however, it is possible to outline several broad features which should be included in any plan of management of rheumatoid arthritis in children.

1. *Adequate Care and Follow-Up.*—Clinical responsibility for children with rheumatoid arthritis must not be shifted from department to department, and follow-up must be adequate. Attempts to trace

23. Access was possible through the courtesy of Dr. Otto Steinbrocker.

these children showed that almost without exception they sought treatment at more than one hospital, that periods of intensive study led to no clinical progress, that periods of extensive therapy were frequently followed by periods of no therapy at all and finally that the patients progressed through three or four different clinical specialties with no correlation or follow-up on the part of any of the persons involved. It would seem that a central agency for the purpose of classifying and following all cases of rheumatic disease in children in a given community would prove of immense value.

2. *Rest.*—The fundamental feature of any program of treatment of rheumatoid arthritis in children is rest. The study of approximately 50 cases has shown no instance of exacerbation during the active phase of the disease in any child hospitalized and given complete rest over a period of thirty days or more. In no instance has the incidental disuse of the involved extremities resulted in further loss of previously restricted motion in the joints. On the contrary, the records show that all too frequently improvement led to early abandonment of rest, with deleterious effects. There were 6 well documented instances of exacerbation of the disease while the patient was under direct institutional observation as a consequence of too early mobilization. Under prolonged rest each child showed subjective improvement and natural inclination to increased activity of the joints.

The use of rest must be clarified and defined. It means absolute rest in bed, but it does not mean mummification of the patient or his parts. Limited exercise may be carried on. Active motion of the joints will more or less depend on the pain involved in carrying out movement. In a broad way, it will be occupational or diversionary in contradistinction to supervised physical therapy, because the latter tends to be too vigorous. Two instances occurred in which physical therapy resulted in definite exacerbation during hospitalization, 1 as a result of weight-bearing exercises and 1 following pool therapy. Measures effective in adults do not necessarily apply to children. Inasmuch as ankylosis does not usually occur and motion is regained without intervention, the need for physical therapy is less urgent. The one deleterious effect which has been observed to follow prolonged immobilization is the destruction of the femoropatellar cartilage resulting from persistent extension of the knee. On the whole, it must be realized that in the face of advancing disease neither forced active motion nor passive manipulation, in or out of the water, will serve to stave off the increasing muscle spasm; the less the involved joints are disturbed in children, the sooner function will be regained.

To obtain rest, simple orthopedic measures are a useful adjunct in the active phase. When the muscles of the knees, for example, demonstrate spasm and motion is painful, a simple Buck's extension

will relieve sign and symptom. Of all plaster apparatus, the most useful is the cock-up splint applied to the wrist to obtain relaxation of the long extensor muscles. It must be applied in a position of comfort, and increased dorsiflexion will be gained by repeated application.

Braces must be used logically and purposefully. It is an old orthopedic adage that braces will not straighten a crooked limb, nor will the brace modify the deleterious effects of exercise if weight-bearing activity is basically harmful. When a child is ready to walk by reason of quiescence of his disease, he will not require a brace except for the support of a joint whose ligaments have been found to be relaxed in consequence of the disease. A light Goldthwaite type of brace has been found to be useful when applied to the backs of children in whom serious postural defects have developed in consequence of general muscular disability. This is used in conjunction with postural training and it is in answer to this aspect of the problem that physical therapy has been found to be most useful.

3. *Manipulation.*—Six patients in this series were subjected to forceful manipulations of joints, some of them repeatedly. In none was there any evidence of permanent gain in the direction of normal alignment or motion. On the contrary, the records indicate that following such treatment deformity reoccurred on release of pressure. The significance of trauma has been pointed out, and forceful manipulation can only be regarded as a traumatizing procedure.

4. *Focal Infection.*—There is no basis for fear in the attack on focal infection during the active phase as distinguished from the prodromal phase of the disease. Ten patients were subjected to surgical treatment of the upper respiratory passages during the active stage of the disease, without exacerbation of arthritis. On the other hand, in 5 cases the disease was originally precipitated by such treatment. It should be added that the outcome in the 5 cases was good. In regard to focal infection, the outcome of the arthritic disease in general was best in cases in which no focal infection existed. It was poorest when focal infection was unsuccessfully or repeatedly treated or when there was more than one single incident of focal infection.

5. *Surgical Procedure.*—Major operative treatment was attempted in 6 instances in this series. In 2 cases the knee joints were surgically fused. Examination of the synovia at operation indicated in both cases that active inflammation was present. Within a period of four months following operation acute exacerbation of the arthritic process developed in the 2 children involved. The causal relationship of the flare-up to the operative attack is debatable, but the crippling which ensued did render the reconstructive procedures useless to the patient. Synovectomies of the knees have been attempted four times in this series. One

resulted in ankylosis. In 1 case the patient was subjected to synovectomy at a time when there was active arthritis of about equal severity in the two knees. The knee operated on yielded the poorer result. The other two synovectomies were carried out on the same child at a time of quiescence of the arthritic disease. Fairly good motion was obtained but was useless since the child was unable to walk for other reasons. Certainly the results of surgical intervention carried out during the active stage of the disease have not been encouraging. Whether reconstruction is feasible after several years of quiescence has not yet been demonstrated, although recent experience in this field has been encouraging. This will form the basis of a future report.

6. *Medical Treatment.*—There are no reports of the controlled use of salicylates in the treatment of rheumatoid arthritis in children. Chrysotherapy in children has been extensively reported by Coss and Boots. Coss is quoted:

> In a series of 51 cases 22 were treated with gold and 29 by [other] methods. Fifty-three per cent [of gold-treated patients] showed moderate to marked improvement [as compared with] 75 per cent of the non-gold-treated patients [showing improvement]. This suggests that gold . . . is . . . ineffective. Actually the gold-treated patients were those with very active disease in whom all other treatment methods failed. We [still] feel that a trial of gold is indicated after a reasonable period of time [six to twelve months] . . . in the event of failure to secure clinical improvement with other methods.

Coss observed toxic reactions to the drug in 10 of the 22 children receiving chrysotherapy. The reactions were of mild degree in all save 1 patient, in whom toxic hepatitis was reported to have developed.

RESULTS

In 35 cases the end results were as follows: 1. Three patients died, the cause of death being (*a*) amyloidosis, (*b*) undetermined and (*c*) congestive heart failure. 2. Seven patients were left with severe residual crippling, 2 were moderately crippled, 2 were minimally crippled and 14 recovered without residual crippling. 3. In 7 patients the disease was still active at the time of last observation, and of these, 2 were severely crippled, 4 moderately crippled and 1 minimally crippled.[24]

Table 4 presents the end results in this series compared with those reported by Colver.

24. Severe crippling means either practical or utter impairment of locomotion or loss of the use of an upper extremity, moderate crippling means major derangement of a major joint without loss of function of the limb involved, i. e., ankylosis of the elbow in a good functional position, and minimal crippling means major impairment of a minor joint or minor impairment of a major joint.

COMMENT

Further study of rheumatoid arthritis in children may modify the conclusions which have been based on only 35 cases; yet there is the feeling that the survey has been sufficiently broad to justify the working concept which has been presented.

The mechanical aspects of the disease have been presented in some detail because study of the records has indicated that perhaps pediatricians and rheumatologists have not been sufficiently tolerant of the fact that rheumatoid arthritis is a systemic disease which primarily involves the locomotor system.

Coss and Boots observed the disease in patients younger than those in the cases reported in this paper. The differences are not irreconcilable.

TABLE 4.—*End Results in the Cases Studied as Compared with Those in Colver's Cases*

	(1) Colver	(2) Present Series	Composite (1 + 2)
Number of cases	49	35	84
Dead	12 (24.5%) (2 from streptococcic septicemia, 1 from amyoid, 1 from urinary infection, 1 from pericarditis and 7 from unknown causes)	3 (8.6%) (1 from unknown causes, 1 from amyloid and 1 from congestive failure)	15 (17.8%)
Inactive	19 (38.8%)	25 (74.3%)	44 (52.3%)
Severely crippled	2 (4%) (unable to earn livelihood)	7 (14.3%)	9 (10.7%)
Moderately crippled	6 (12.2%)	2 (5.7%)	8 (9.6%)
Mildly crippled	4 (8.1%)	2 (5.7%)	6 (5.2%)
Completely recovered	7 (14.3%)	14 (40%)	21 (20%)
Active	18 (38.7%)	7 (20%)	25 (27.7%)
Severely crippled *	..	4	
Moderately crippled *	..	2	
Mildly crippled *	..	1	

* Data in relation to this were not tabulated for Colver's cases.

The material in this paper which was taken from the New York Hospital closely follows that of Colver and of Coss. In a children's medical service acute forms of the disease in young children are more frequently encountered. However, such material is in itself incomplete, since it does not take cognizance of the many cases of mild disease nor does it embrace the considerable number of partially crippled children who are treated in the orthopedic units.

Of the 35 cases available for study of the end results, only 5 might be said to come within the category of so-called Still's disease by virtue of conformation to the original description of Still's cases. It would seem preferable to consider chronic nonspecific disease of the joints in children as rheumatoid arthritis, realizing that in a small number of cases the disease is severe, deforming and accompanied with visceral lesions.

Of the 35 patients, 14, or 40 per cent, are completely well. Some of the 14 have reached adult life. Of those reaching adult life, 2 have experienced recrudescence after puberty. These two occurrences would indicate that although any individual "attack" of rheumatoid arthritis may be said to be quiescent, the arthritic "status" persists even in the absence of any arthritis. In this sense, a "cure" of the attack may have been accomplished, but the potential abnormal reaction of any of these predisposed persons to some future injury is not altered. In regard to adult function of the joints of children in whom permanent damage has resulted, it may be anticipated that secondary degenerative changes will sooner or later be imposed on the original inflammatory process, and this will be in direct proportion to the extent of the original destruction and to the mechanical activity of the particular joint involved.

With reference to treatment of rheumatoid arthritis in children, this paper has argued for no particular scheme of management save rest. On the contrary, it has attempted to demonstrate the course of the disease irrespective of therapy on the basis of which any specific progress might be evaluated. It is readily seen that such an evaluation must take into consideration the chronicity of the disease plus the fact that if the patient is seen early there is no means of foretelling when the disease will naturally react violently and progressively and when it will subside regardless of treatment. Successful treatment must be gaged by the following criteria: (1) shortening of the duration of active inflammation, (2) control of spread to previously uninvolved joints and (3) prevention of relapse in the quiescent period.

SUMMARY

The records of some 200 children suffering from rheumatoid arthritis have been studied.

Thirty-five cases have been followed for sufficiently long periods to enable study of the end results. Etiologic factors in these cases appear to have been (1) infection, (2) trauma and (3) allergy. The essential feature of the disease is an altered specific reaction of the patient to these activating agents.

There is essential agreement with the conclusion of Colver that the disease is self limited. There is essential disagreement with the same author in regard to the "second attack" or recrudescence after quiescence.

Study of the results obtained after the involvement of various joints by the rheumatoid process indicates a wide difference in the outcome to be anticipated according to the joint involved, being poorest in the elbows, the carpal joints and the wrists and relatively good in the ankles and the knees.

Visceral lesions accompany the severe forms of the disease, the lesions of greatest importance being "rheumatism-like" lesions in the heart and

amyloid degeneration in the liver and spleen. Clinical evidence of cardiac disease is present in some of the most severe cases.

A persisting monarticular form of rheumatoid arthritis in children may be sometimes observed and is difficult to distinguish in some cases from tuberculous synovitis. Rheumatoid arthritis and rheumatic fever may closely resemble one another.

There is a reasonably good basis for the removal of focal infection during the active phase of the disease. Surgical attack on joints during the active phase of the disease has not been followed by sufficiently good results in the cases studied to make it an advisable undertaking.

The incidence of recovery is in truth high if all cases are taken into consideration.

ACUTE PANARTERITIS IN ALLERGIC PERSONS

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THE ROLE of hypersensitivity in acute arterial disease has been emphasized by Rich.[1] We have recently seen 2 patients with acute arteritis, and both had definite atopy. In 1 the arterial disease was not diagnosed until the necropsy was performed. In the other, who had an acute angiitis accompanied with severe exacerbation of an allergic dermatitis, the diagnosis was made during life, recovery probably being favored by the demonstration of the underlying pathologic process. In addition to the theoretic interest, therefore, it is hoped that an increasing awareness of this syndrome will have practical applications in clinical diagnosis and treatment.

REPORT OF CASES

CASE 1.[2]—J. K., a 40 year old white farmer, was seen in the dermatology department in April 1946. He complained of perianal itching of two years' duration and a pruritic eruption around the perineum of nine months' duration. Scratch tests and a test diet showed that he was sensitive to eggs, and he improved on an egg-free diet plus roentgen therapy of the cutaneous lesions. Five months later he inadvertently ate some cake containing eggs and suffered an acute exacerbation of the perineal lesion, followed by severe conjunctival edema and congestion. Two days later there appeared a red papular rash on the thighs, and this soon became generalized. He was hospitalized in another city and improved after local therapy and some medication, the nature of which is unknown. One week after returning to work, however, he had another exacerbation and was admitted to our hospital.

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1. (*a*) Rich, A. R.: The Role of Hypersensitivity in Periarteritis Nodosa, Bull. Johns Hopkins Hosp. **71**:123, 1942; Additional Evidence of the Role of Hypersensitivity in the Etiology of Periarteritis Nodosa, ibid. **71**:375, 1942; (*b*) Hypersensitivity to Iodine as a Cause of Periarteritis Nodosa, ibid. **77**:43, 1945. (*c*) Rich, A. R., and Gregory, J. E.: The Experimental Demonstration That Periarteritis Nodosa Is a Manifestation of Hypersensitivity, ibid. **72**:65, 1943. (*d*) Rich, A. R., and Follis, R. H., Jr.: Studies on the Site of Sensitivity in the Arthus Phenomenon, Bull. Johns Hopkins Hosp. **66**:106, 1940. (*e*) Rich, A. R.: The Role of Hypersensitivity in the Pathogenesis of Rheumatic Fever and Periarteritis Nodosa, Proc. Inst. Med. Chicago **15**:270, 1945.

2. This case was used through the courtesy of Dr. Stephan Epstein.

The family history revealed that two sisters had eczema, while a third had severe urticaria when she ate strawberries.

Physical examination revealed nothing noteworthy except for the generalized subacute dermatitis. The blood pressure was 150 systolic and 80 diastolic. The laboratory findings were entirely normal.

Course in Hospital.—Under a regimen of local therapy, administration of tripelennamine hydrochloride and an egg-free diet, the dermatitis improved. However, four days after his admission to the hospital the patient began to complain of abdominal distention and nausea. This was followed by vomiting and generalized pain in the upper abdominal area. At this time the white blood cell count had risen to 25,900 per cubic millimeter. On physical examination the picture was that of an acute abdominal condition, and exploratory laparotomy was advised.

At operation the only abnormality found was a moderately inflamed appendix, which was removed. Pathologic examination showed a subacute appendicitis.

The patient was given routine postoperative care. On the second postoperative day his temperature rose to 99.6 F. and there was a recurrence of the abdominal pain and nausea. The next day he had severe crampy abdominal pain, vomiting and three loose stools consisting of thin, reddish brown foul fluid. The fluid gave a strongly positive reaction for blood by the benzidine test, as did the vomitus. The urine, which had previously been normal, now contained 400 mg. of albumin per hundred cubic centimeters, with many leukocytes and red blood cells in the sediment as well as many waxy, cellular and granular casts.

On the seventh postoperative day the sutures were removed, and that afternoon the wound suddenly disrupted with evisceration. The peritoneal cavity contained a large amount of brownish fluid. About 3 feet (0.9 meter) of ileum was found to be indurated and in part gangrenous. This was resected.

Pathologic Examination.—The specimen examined consisted of 80 cm. of small bowel. The wall was indurated and thickened in a patchy fashion. In these areas the mucosa was essentially normal except for marked hyperemia. Microscopically there was focal gangrene of the wall. The striking lesion was widespread necrosis of the arterioles in the mesentery and in the bowel wall (fig. 1). These showed massive infiltration into all coats, with a pleomorphic cellular exudate composed chiefly of polymorphonuclear cells. There were only a few eosinophils. The media showed varying degrees of necrosis. Many of the arterioles were occluded by recent thrombi.

The pathologic diagnosis was focal gangrene of the ileum on the basis of visceral angiitis.

Postoperative Course.—The postoperative course was uneventful. The dermatitis gradually disappeared, but the urine continued to show definite abnormalities. One month after operation the amount of albumin in the urine was 30 mg. per hundred cubic centimeters, with leukocytes, red blood cells and casts of many types in the sediment. Three months later a phenolsulfonphthalein test of renal function showed a 55 per cent total excretion of dye. Up to the time of the writing of this article there has been no elevation of the blood pressure.

Comment.—The gangrene of the bowel in this patient with acute allergic dermatitis was thought to be on the basis of an acute arteritis. The evidence of acute renal damage coincident with the abdominal condition, plus the residual renal damage, leads us to suppose that there was simultaneous arterial involvement in the kidneys and possibly in other organs.

Case 2.—F. G., a 67 year old white farmer, was first seen in August 1946, with a chief complaint of pain in the chest and abdomen. Eight months previously he

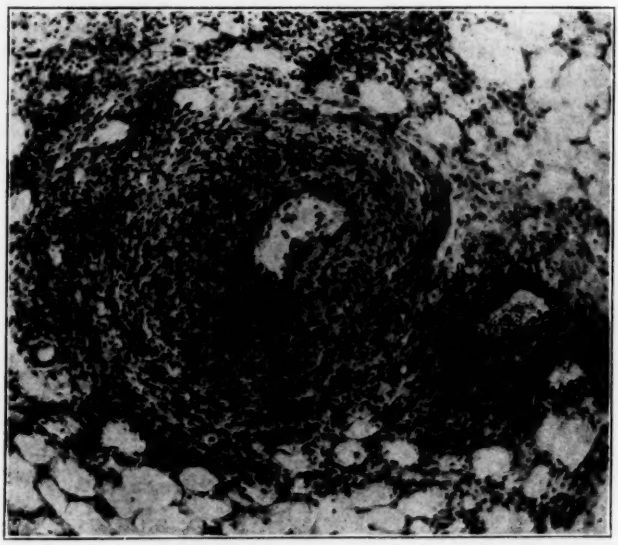

Fig. 1 (case 1).—Photomicrograph showing the acute arteritis in a mesenteric arteriole. Hematoxylin and eosin stain; × 70.

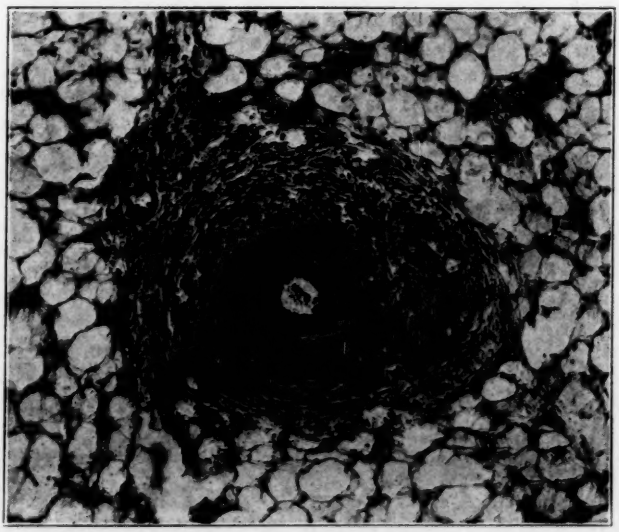

Fig. 2 (case 2).—An arteriole in the periadrenal fat. Hematoxylin and eosin stain; × 70.

had had pneumonia, which had been treated with one of the sulfonamide compounds. He recovered fully and felt well until March 1946, when he began to feel weak, nervous and mentally depressed and noted severe anorexia. In May 1946 he began

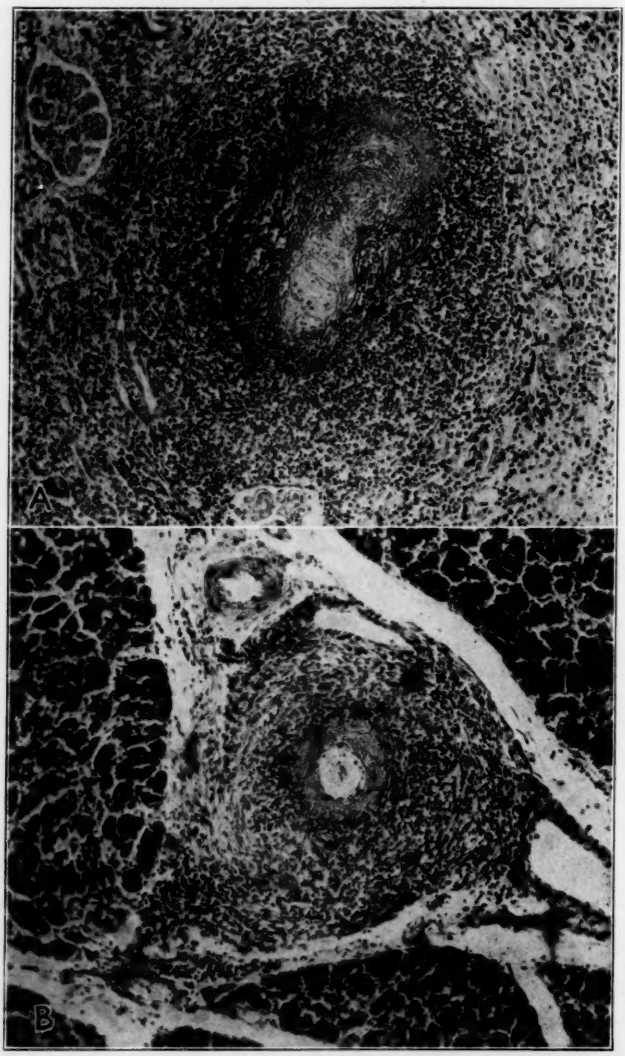

Fig. 3 (case 2).—*A*, kidney; the fibrinoid necrosis in the media is striking, and there is recent thrombosis. *B*, pancreas. Hematoxylin and eosin stain; × 70.

to have severe abdominal pain. There was a total loss of weight of about 30 pounds (13.6 Kg.) in six months.

Previous to August 1946 he had been seen many times in the dermatology department because of severe asthma and allergic dermatitis. The past history was otherwise noncontributory. No familial history of allergy was obtained.

Physical examination on admission revealed no abnormalities. The blood pressure was 150 systolic and 90 diastolic. The patient did not appear ill.

Laboratory Findings.—On admission of the patient to the hospital the urine showed a specific gravity of 1.015, and the highest reading ever obtained was 1.019. The albumin content was 200 mg. per hundred cubic centimeters, and the sediment contained leukocytes, red blood cells and many casts of the hyaline, waxy, vacuolated and granular type. These findings persisted. A modified Mosenthal renal function showed severe renal damage. The blood on admission showed a hemoglobin content of 11.7 mg. per hundred cubic centimeters, a red blood cell count of 4,660,000 and a white blood cell count of 16,700, with 84 per cent segmented cells, 12 per cent lymphocytes, 2 per cent eosinophils and 2 per cent monocytes. The nonprotein nitrogen content was 35 mg. per hundred cubic centimeters. The total plasma protein was 5.7 Gm. per hundred cubic centimeters. Later there was a progressive drop in blood hemoglobin and in the red blood cell count and hypoproteinemia which reached a level of 3.98 Gm. per hundred cubic centimeters. Examination of the stool, gastric analysis and roentgenologic studies revealed nothing significant.

Course in Hospital.—The course was progressively downhill. The temperature rose to 101 to 103 F. The hypoproteinemia became severe in spite of the intravenous administration of large quantities of plasma. The patient complained persistently of abdominal pain, and distention was severe. Terminally he became disoriented, showed signs of decompensation and had a few mild convulsive seizures. He died one month after his admission to the hospital.

Autopsy.—A complete necropsy was performed, but only the main findings are given. The chief lesion was a generalized panarteritis (figs. 2 and 3), most severe in the lungs, liver, pancreas, adrenals, kidneys and prostate. Histologically the arterioles showed more involvement than the large arteries. There was extensive cellular infiltration, not only around the vessels but also into the media and intima. Lymphocytes and large mononuclear cells were predominant, with a few plasma cells and eosinophils. There was fibrinoid necrosis of the arteriolar walls, with destruction of the elastic laminas. The vascular necrosis was most severe in the kidneys and liver. One of the branches of the hepatic artery contained a completely organized thrombus, while many of the other vessels contained fresh thrombi.

Final Anatomic Diagnosis.—The final anatomic diagnosis was: visceral angiitis (panarteritis, periarteritis nodosa), glomerulonephritis on the basis of visceral angiitis, pleural adhesions, hydrothorax, ascites, fibrous obliterative pericarditis, passive congestion of the lungs, spleen and liver and moderate generalized arteriosclerosis in a patient who had had a history of atopy.

COMMENT

Many theories have been advanced as to the cause of periarteritis nodosa, recent evidence favoring the concept that it is the result of hypersensitivity. This theory was first suggested by Gruber in 1923,[3] but at that time there was little to support it. In 1937 Clark and Kaplan [4]

3. Gruber, G. B.: Zur Frage der Periarteritis nodosa, mit besonderer Berücksichtigung der Gallenblasen-und Nieren-Beteiligung, Virchows Arch. f. path. Anat. **258**:441, 1923.

4. Clark, E., and Kaplan, B. I.: Endocardial, Arterial and Other Mesenchymal Alterations Associated with Serum Disease in Man, Arch. Path. **24**:458 (Oct.) 1937.

reported the observance at autopsy of lesions similar to periarteritis in 2 patients who had received serum therapy for lobar pneumonia and in whom serum sickness had developed shortly before death. These authors were reluctant to point to a causal relationship between the serum sickness and the arterial lesions. Eason and Carpenter,[5] also in 1937, in a paper on the treatment of rheumatic fever with antiscarlatinal serum, reported that in 1 of the treated patients in whom death followed serum sickness the lesions of periarteritis nodosa were found at autopsy. They felt that in the presence of rheumatic infection it was difficult to relate the vascular lesions to the serum sickness.

More recently, Rich [1a, b] has brought forth some definite evidence that these arterial lesions are related to hypersensitivity. He has not only reported the occurrence of panarteritis in 7 persons treated with serum and sulfonamide compounds, but has also stated that in 1 case a biopsy taken before serum sickness appeared showed no arterial lesions while tissues studied after did show typical arteritis. Rich and Gregory [1c] later succeeded in producing the lesions in rabbits made hypersensitive to horse serum.

With these observations in mind, corollary evidence is not difficult to find. For example, it is generally accepted that the pathologic process in the Arthus phenomenon is primarily that of vascular damage [6] and that the changes in the vessel wall, from the early edema to the terminal necrosis, can also be found in periarteritis nodosa if cases are studied in which the disease is of different duration. Also, many observers have noted that significantly more persons with asthma succumb to periarteritis nodosa than would be expected.[7] In 1943 Reimann [8] reported periarteritis nodosa in 2 cases of trichinosis, significant in view of the high degree of hypersensitivity produced by the antigen in this disease. Necrotizing arteritis has also been reported in a fatal case of Loeffler's syndrome [9] and in an instance of hypersensitivity to iodine.[1b]

5. Eason, J., and Carpenter, G.: Treatment of Acute Rheumatic Polyarthritis with Concentrated Antiscarlatinal Serum, Quart. J. Med. **30**:93, 1937.

6. Gerlach, W.: Studien über hyperergische Entzündung, Virchows Arch. f. path. Anat. **247**:294, 1923. Rich and Follis.[1d]

7. Rackemann, F. H., and Greene, J. D.: Periarteritis Nodosa and Asthma, Tr. A. Am. Physicians **54**:112, 1939. Kline, B. S., and Young, A. M.: Cases of Reversible and Irreversible Allergic Inflammation, J. Allergy **6**:258, 1935. Kallos, P., and Kallos-Deffner, L.: Die experimentellen Grundlagen der Erkennung und Behandlung der allergischen Krankheiten, Ergebn. d. Hyg., Bakt., Immunitätsforsch. u. exper. Therap. **19**:178, 1937.

8. Reimann, H. A.; Price, A. H., and Herbut, P. A.: Trichinosis and Periarteritis Nodosa, J. A. M. A. **122**:274 (May 29) 1943.

9. Bayley, E. C.; Lindberg, D. O. N., and Baggenstoss, A. H.: Loeffler's Syndrome: Report of a Case with Pathologic Examination of the Lungs, Arch. Path. **40**:376 (June) 1945.

The occurrence of prodromal infection is common in periarteritis nodosa,[10] and this focuses attention on the role of bacterial allergy. Peale and others [11] reported a case of periarteritis nodosa complicating scarlet fever, and it is noteworthy that in addition their patient had a history of allergy as evidenced by the appearance of hives following the eating of tomatoes. Metz [12] produced the lesions experimentally with foreign protein and streptococci, and Gerber [13] succeeded in producing arterial necrosis by repeated intravenous administration of bacterial filtrates. Masugi and Isibasi [14] did the same by sensitization with bacteria.

Attempts to produce experimental hypersensitivity to the sulfonamide drugs have failed, probably because the antigen involved is a sulfonamide–plasma protein combination.[15] Nevertheless, many of the studies on anatomic lesions due to damage caused by sulfonamide compounds [16] indicate the frequent occurrence of arterial lesions in instances of such damage.

It seems, therefore, that a variety of antigens may be responsible, provided that the "soil," about which little is known, is predisposed to react by showing vascular damage. Indeed, vascular disease in the broad sense is still poorly understood. Arterial lesions in certain clinical syndromes are anatomically so similar that it has properly been suggested that the term "visceral angiitis" be used for the whole group. The suspicion has frequently been expressed that there is a basic factor common to rheumatic fever, periarteritis nodosa, anaphylactoid purpura, lupus erythematosus, scleroderma, dermatomyositis and glomerulonephritis.[17] These conditions are of course less common than vascular

10. Spiegel, R.: Clinical Aspects of Periarteritis Nodosa, Arch. Int. Med. **58**:993 (Dec.) 1936.

11. Peale, A. R.; Gildersleeve, N., and Lucchesi, P. F.: Periarteritis Nodosa Complicating Scarlet Fever, Am. J. Dis. Child. **72**:310 (Sept.) 1946.

12. Metz, W.: Die geweblichen Reaktionserscheinungen an der Gefässwand bei hyperergischen Zuständen und deren Beziehungen zur Periarteritis nodosa, Beitr. z. path. Anat. u. z. allg. Path. **88**:17, 1932.

13. Gerber, I. E.: The Schwartzman Phenomenon in the Kidneys of Rabbits: Observations on Effects of Intravenous Administration of Bacterial Filtrates, Arch. Path. **21**:776 (June) 1936.

14. Masugi, M., and Isibasi, T.: Ueber allergische Vorgänge bei Allgemeininfektion vom Standpunkt der experimentellen Forschung, Beitr. z. path. Anat u. z. allg. Path. **96**:391, 1936.

15. Schönholzer, G.: Die Bindung von Prontosil und die Bluteiweiskörper, Klin. Wchnschr. **19**:790, 1940.

16. Black-Schaffer, B.: Pathology of Anaphylaxis Due to Sulfonamide Drugs, Arch. Path. **39**:301 (May) 1945.

17. Banks, B. M.: Is There a Common Denominator in Schleroderma, Dermatomyositis, Disseminated Lupus Erythematosus, the Libman-Sacks Syndrome and Polyarteritis Nodosa? New England J. Med. **225**:433, 1941. Klemperer, P.; Pollack, A. D., and Baehr, G.: Pathology of Disseminated Lupus Erythematosus, Arch. Path. **32**:569 (Oct.) 1941. Rich.[16]

disease of a "degenerative" nature, but whether or not arteriosclero is is truly degenerative remains to be proved. Perhaps the evidence presented by Holman [18] for a dietary factor in the production of necrotizing arteritis in dogs will help to bridge this gap.

In any case, there is now enough evidence to show that the relationship between hypersensitivity and acute arterial disease is more than accidental. We feel confident that more and more of these cases will be recognized before autopsy is performed. In our case 1 all medication was stopped as soon as the diagnosis was made, in the hope that the antigen might be excluded by such means. This may be a life-saving measure when the antigen is exogenous. It is to be hoped that new developments in the field of the antiallergic drugs will lead to a more active method of therapy in the near future.

SUMMARY

Two cases of acute necrotizing arteritis in persons with atopy have been observed. In 1 case the condition was diagnosed early in the course of the illness, all medication stopped and a good recovery made.

The importance of the role of hypersensitivity in acute arterial disease is emphasized, and the possible clinical implications are discussed.

18. Holman, R. L.: Acute Necrotizing Arteritis, Aortitis, and Auriculitis Following Uranium Nitrate Injury in Dogs with Altered Plasma Proteins, Am.J.Path. **17**:359, 1941; Necrotizing Arteritis in Dogs Related to Diet and Renal Insufficiency: V. Evidence for a Dietary Factor, ibid. **19**:977 (Nov.) 1943.

Progress in Internal Medicine

SYPHILIS

A Review of the Recent Literature

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(Continued from Page 690)

Bismuth Preparations.—Eagle [106] has studied the toxicity and therapeutic efficacy in experimental syphilis in rabbits of three representative bismuth compounds—sodium and potassium bismuthotartrate ("bismosol"), serving as a prototype of the water-soluble bismuth compounds, a-carboxyethyl-b-methyl-bismuthononoate ("biliposol"), representative of fat-soluble compounds, and bismuth subsalicylate in oil, the preparation which has been most widely used in the treatment of syphilis. All these three preparations were given intramuscularly, a single injection being given approximately six weeks after intratesticular inoculation.

The results indicate that all three types of bismuth preparations studied are, mol for mol, from one half to two thirds as active therapeutically as is oxophenarsine hydrochloride similarly administered in a single injection in the treatment of experimental syphilis in rabbits. By virtue of their lower toxicity, two of the compounds, bismuth subsalicylate in oil and biliposol, provided margins of safety between the effective and toxic levels from six to eight times greater than that provided by oxophenarsine hydrochloride.

Voss and Tatum [107] present experimental data suggesting that in rats paraaminobenzoic acid exerts a low grade protection against the toxic action of such bismuth preparations as sodium bismuthyl citrate, sodium bismuthyl mannonate and sodium bismuthyl tartrate.

Bismuth Gingivostomatitis.—The prevention of gingivostomatitis during administration of bismuth is discussed by Scopp.[108] In this

106. Eagle, H.: The Relative Toxicity and Therapeutic Activity in Experimental Syphilis of Bismuth Subsalicylate, Bismosol and Biliposol, Am. J. Syph., Gonor. & Ven. Dis. **30**:549 (Nov.) 1946.

107. Voss, E., and Tatum, A. L.: Protective Action of *p*-Aminobenzoic Acid Against Certain Bismuth Preparations, J. Pharmacol. & Exper. Therap. **90**:161 (June) 1947.

108. Scopp, I. W.: Bismuth Gingivo Stomatitis, Mil. Surgeon **99**:196 (Sept.) 1946.

dentist's experience, the bismuth line rarely occurs when there is good oral hygiene. Bismuth is deposited when there is vascular stasis and is especially common in the presence of gingivitis, tartar or pyorrhea pockets.

Arsenical Preparations.—Dichlorophenarsine hydrochloride (3-amino-4-hydroxyphenyldichloroarsine hydrochloride), an arsenoxide which in solution yields phenarsine oxide ("mapharsen") has been established as a safe and therapeutically effective arsenical. Beerman and Wammock [109] report that the buffer which is added to dichlorophenarsine hydrochloride may be a factor in the low toxicity of this preparation. These workers suggest that the addition of sodium ascorbate somewhat lessens its toxicity without decreasing therapeutic effectiveness.

Tryparsamide: From a comprehensive review of the use of tryparsamide in syphilotherapy, Koteen [110] concludes:

1. Because pharmacologic studies show that pentavalent arsenicals, including tryparsamide, are not therapeutically effective until reduced to the trivalent form and do not posses greater penetrability or affinity for the central nervous system than the trivalent drugs, one cannot expect that tryparsamide will be an effective chemotherapeutic agent for the treatment of syphilis.

2. Tryparsamide often causes permanent visual damage in spite of detailed precautionary measures. This is especially true in patients with tabes dorsalis.

3. Considerable variation in the therapeutic results attributable to tryparsamide is evident throughout many reports. Patients with neurosyphilis treated in this clinic failed to substantiate the reported therapeutic efficacy of the drug.

4. There are alternative methods for treating all forms of neurosyphilis in which tryparsamide is said to be of value, and none of these regimens is as dangerous as one employing tryparsamide.

Toxic Effects of Arsenical Compounds.—The most recent compilation of the United States Navy statistics regarding reactions to arsenicals has been made by Burton, Justyn and Anderson.[111] After the administration of 1,394,868 doses of neoarsphenamine (1925 to 1945) there were 55 deaths, mostly due to hemorrhagic encephalitis and exfoliative dermatitis, a ratio of 1 death to every 35,361 injections. After 1,115,873 injections of oxophenarsine hydrochloride (1935 to 1945) there were 7 deaths, a ratio of 1 death to every 159,410 injections.

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109. Beerman, H., and Wammock, V. S.: Dichlorophenarsine Hydrochloride in the Treatment of Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **31**:150 (March) 1947.

110. Koteen, H.: The Present Status of Tryparsamide in Syphilotherapy, Am. J. M. Sc. **213**:611 (May) 1947.

111. Burton, O. L.; Justyn, G. W., and Anderson, L. T.: Toxic Effects of Arsenical Compounds as Employed in the Treatment of Syphilis in the United States Navy, 1945, U. S. Nav. M. Bull. **47**:180 (Jan.-Feb.) 1947.

Arsenical Encephalopathy: Prebble [112] has made an extensive review of the subject of arsenical encephalopathy and has reported 187 cases, more than the total previously reported.

Of 75 cases described in the literature, 57 were fatal. The onset of symptoms occurred after a varying number of arsenical injections but most often early, i. e., after the second or third injections. The commonest history was found to be as follows:

> Intense headache is the initial symptom and may be accompanied by fever, shivering and vomiting. On the following day the patient suddenly has an epiliptiform convulsion, with clonic spasms, followed by unconsciousness. The deep reflexes are lost; a positive Babinski's sign is present; squint and various other signs indicative of involvement of the central nervous system may occur. Retention of urine is common. Epileptiform convulsions recur at intervals, and coma continues until death. A fatal result often supervenes within 48 hours of the onset of symptoms.

The exact incidence of arsenical encephalopathy is unknown. It is obviously, from this author's large series, more frequent among patients treated in India. It has been observed with greater frequency since the introduction of massive arsenotherapy. Here it has occurred in 1 in every 113 patients treated, and the incidence of fatal cases has been 1 in every 268. Several writers have noted that pregnancy apparently adds to the risk of this reaction.

The several theories of causation are discussed. The author is inclined to the view that individual idiosyncrasy is a possible but unsatisfactory explanation. He favors rather the theory indicating a direct toxic action of arsenicals on the capillaries of the brain, stressing pathologic evidences of damage to the structures and noting that the arsenic content of the brain may be higher in patients with encephalopathy than in those who have been similarly treated but who die from other causes.

Treatment of the reaction is unsatisfactory. The most useful remedies are thought to be morphine, epinephrine hydrochloride and glucose in isotomic solution of sodium chloride. Vitamin B and oxygen are suggested as being of value. In this author's experience, 2,3-dimercaptopropanol (BAL) appeared to have little influence on the condition. Because bronchopneumonia is a frequent complication, it is considered to be important to nurse comatose patients in the Fowler position.

Agranulocytosis: Eleven cases in which agranulocytosis occurred during intensive arsenotherapy for syphilis are reported by Fisher,

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112. Prebble, E. E.: Arsenical Encephalopathy: A Review of the Literature with a Report of a Further One Hundred and Eighty-Seven Cases, Brit. J. Ven. Dis. **22**:93 (Sept.); 139 (Dec.) 1946.

Holley and Fein.[113] In all cases the reaction occurred toward the end of the scheduled course of treatment. Prompt cessation of arsenical administration and therapy with dimercaprol, "pentnucleotide," liver extract and, in the more severe cases, blood transfusions sufficed to prevent mortality. The importance of careful observation of patients receiving intensive arsenotherapy is emphasized, regulation of body temperature and routine leukocyte counts being considered especially desirable. In 50 per cent of the patients described, agranulocytosis occurred after there had been a febrile reaction of the "ninth day erythema" type.

The Milian Reaction: An extensive review of the reaction commonly referred to as "the ninth day erythema of Milian" has been made by Binazzi,[114] who reports ninety-one such reactions. The reaction is thought to be an expression of an anaphylactic state of intolerance to the arsenical drugs accompanied with imbalance of the autonomic nervous system. In this author's experience, the Milian reaction occurred more frequently in women than in men and most often in patients with early syphilis under arsenical treatment for the first time. The concomitant administration of sulfonamide compounds appeared to increase the incidence. The author stresses the constitutional manifestations—anorexia, nausea, vomiting, headache, sore throat, lymphadenopathy, conjunctival suffusion, pruritis, musculoskeletal pains and fever. He recommends that antisyphilitic therapy be suspended for twenty to forty days and that at the end of this time arsenotherapy be resumed with great caution.

The Jarisch-Herxheimer Reaction: Giberti[115] reports that in a patient with an endourethral chancre acute urinary retention developed forty-eight hours after the institution of antisyphilitic therapy with an arsenical and bismuth. He attributes this complication to a Jarisch-Herxheimer reaction.

Semi-Intensive Arsenobismuth Therapy of Early Syphilis.—In July 1942 the United States Army, acting on the recommendation of the Subcommittee on Venereal Diseases of the National Research Council, adopted for routine use a schedule for treating early and latent syphilis with the administration of forty injections of oxophenarsine hydrochloride and sixteen of bismuth subsalicylate in a period of twenty-six weeks. This schedule, a compromise between the more toxic five day

113. Fisher, S.; Holley, H. L., and Fein, G.: Agranulocytosis: Report of Twelve Cases in Which It Followed Intensive Arsenotherapy for Syphilis, Arch. Dermat. & Syph. **55**:57 (Jan.) 1947.

114. Binazzi, M.: Contributo alla conoscenza della sindiome del IX giorno (eritema del IX giorno di Milian), Gior. ital. dermat. e sif. **87**:458 (Dec.) 1946.

115. Giberti, A. Z.: Ritenzione acuta da reazione di Herxheimer in portatore di sifiloma iniziale endourethrale, Arch. ital. dermat., sif. e vener. **19**:138, 1946.

intravenous drip method and the less practicable prolonged schedules used previously, was used during the earlier years of World War II and ultimately was replaced by penicillin therapy.

From an analysis of 3,000 patients with primary or secondary syphilis treated by this twenty-six week schedule, Sternberg and Leifer[116] report that the results in terms of therapeutic effectiveness were "excellent." Of the 2,976 whose status could be appraised, 95.36 per cent had made "satisfactory progress." An apparently favorable outcome was observed in 98.3 per cent of the primary cases in which there was seronegativity, in 94.5 per cent of the primary cases in which there was seropositivity and in 89.3 per cent of the cases of secondary syphilis. A total of 138 patients (4.6 per cent) manifested some form of relapse or reinfection or had positive or doubtful reactions to serologic tests for syphilis at the final examination and were therefore considered to have failed to respond to treatment. There were but 18 (0.64 per cent) in whom the cerebrospinal fluid was abnormal among the 2,842 examined.

In general, the twenty-six week treatment was tolerated well. It is estimated that with this form of therapy in the Army there was 1 death for 33,000 patients treated. There were no deaths from treatment of the 3,000 patients in the reported series, and in only 2 instances was it necessary to abandon arsenical therapy because of untoward reactions.

When a survey was made to determine the regularity with which the twenty-six week treatment was being given in the European Theater, it was found that only about 38 per cent of the patients treated were completing the course of therapy within less than eight months. Accordingly, a trial of a more intensified scheme of arsenobismuth therapy, compressed into a period of twenty days, was undertaken.

Pillsbury and Loveman,[117] who have analyzed the results with this twenty day schedule in a series of 1,343 patients with early and early latent syphilis, conclude that the method yielded "very satisfactory one-year results . . . in terms of achievement of a negative serologic test for syphilis and a negative cerebrospinal fluid." Of the cases followed for one year or more, over-all satisfactory results were obtained in 94.96 per cent, unsatisfactory results in 4.26 per cent and "pending" results in 0.78 per cent.

A total of slightly over 4,000 patients with early syphilis received therapy by this method, and there were no resultant deaths. Approximately 96 per cent of the patients completed the outlined course of

116. Sternberg, T. H., and Leifer, W.: The Treatment of Early Syphilis by the Twenty-Six-Week Mapharsen-Bismuth Schedule, Am. J. Syph., Gonor. & Ven. Dis. **31**:124 (March) 1947.

117. Pillsbury, D. M., and Loveman, A. B.: Six to Twelve Month Follow-Up Results in Early Syphilis Treated by a Twenty-Day Intensive Arsenobismuth System, Am. J. Syph., Gonor. & Ven. Dis. **31**:115 (March) 1947.

therapy. A more detailed report of the untoward reactions encountered during the course of the twenty day schedule of arsenobismuth therapy has been made by Cormia and Blauner.[118] It is apparent from their report that although there were no deaths this intensive schedule is inherently toxic. Among 500 patients untoward reactions of various kinds (cerebral irritation, jaundice, toxic erythema, agranulocytosis, excessive fever, hemorrhagic encephalitis and persistent albuminuria) necessitated the termination of therapy in 4.8 per cent of those treated.

Massive Arsenotherapy for Prenatal Syphilis.—Curtis and Morrow [119] have found massive arsenotherapy a rapid and highly efficient method for the treatment of early syphilis associated with pregnancy. Forty women with syphilis were treated by the intensive intravenous drip of 1,080 to 1,200 mg. of oxophenarsine hydrochloride over periods of five to eight days. In addition, each patient received 260 to 520 mg. of bismuth subsalicylate in oil intramuscularly. Nine patients were treated in the first trimester of pregnancy, 21 in the second trimester and 10 in the third. Thirty-three infants born of these mothers were kept under observation for at least three months, and all were nonsyphilitic. Five could not be followed. Three infants died; none, however, had any evidence of congenital syphilis. Two women who became pregnant a second time after intensive therapy were not retreated and gave birth to normal nonsyphilitic babies. There were no abortions, miscarriages or stillbirths in the entire group. In all mothers who were treated for early (primary or secondary) syphilis seronegativity developed and remained throughout two years of observation. No information concerning the occurrence of toxic reactions is given, although the authors state that "reactions due to the treatment are appreciable" and that "penicillin will probably be as efficacious and much less hazardous."

2,3-Dimercaptopropanol (BAL) in Arsenic Poisoning.—The subject of arsenical toxicity was brought into sharp focus by the introduction of massive arsenotherapy for syphilis. In World War II, despite the increased risk of death or serious symptoms of arsenic poisoning, time-shortened schedules of metal chemotherapy were adopted by our Armed Forces for reasons of military expediency. Shortly thereafter, attention was diverted from the problem by the introduction of penicillin into clinical syphilology. However, certain disadvantages of this drug (the desirability of hospitalization and the limitations of its therapeutic effec-

118. Cormia, F. E., and Blauner, S. G.: Reactions to Twenty-Day Intensive Therapy with Mapharsen and Bismuth with a Note on the Use of BAL in Their Management, Am. J. Syph., Gonor. & Ven. Dis. **31**:135 (March) 1947.

119. Curtis, A. C., and Morrow, G.: The Treatment with Massive Arsenotherapy of Early Syphilis Complicated by Pregnancy, Am. J. Obst. & Gynec. **52**: 284 (Aug.) 1946.

tiveness) circumscribe its general use. Metal chemotherapy continues to be widely used, not only for those treated on an ambulatory basis but as an adjunct to decrease the not inconsiderable number of failures resulting from the use of penicillin alone.

There has also been concern with the lethal effects of arsenic, not in its relation to the treatment of syphilis but as a component of that most feared of war gases, lewisite. In 1939, as part of a program of war research in Peters' laboratory at Oxford, there were initiated investigations which led to the demonstration of the effectiveness of dithiols against the noxious action of arsenic. The study has since been actively pursued in England and in this country.

There is now considerable evidence that the toxicity of arsenicals is related to their ability to combine with essential sulfhydryl groups of certain tissue proteins and thus to block physiologic systems vital to cellular economy. Protection against this action of arsenic may be afforded by compounds containing a competing dithiol capable of forming a ring compound at least as stable as the compound of arsenical with tissue sulfhydryl groups. This fact led to the preparation and testing of several dithiols, one of which, 2,3-dimercaptopropanol (British anti-lewisite, or BAL), has proved highly efficacious not only against lewisite and arsenical compounds used in syphilotherapy but also against the baneful actions of other heavy metals.

Information concerning 2,3-dimercaptopropanol was carefully restricted throughout the war. With the cessation of hostilities, it became possible to publish the accumulated data. A committee composed of representatives of the various groups which had participated in the wartime study of BAL has presented, as a symposium on the dithiols, selected papers of fundamental value. Those dealing with biochemistry have been published in the British *Biochemical Journal*,[120] those relating to toxicology, pharmacology and experimental therapeutics in the *Journal of Pharmacology and Experimental Therapeutics* [121] and those concerned with clinical applications in the *Journal of Clinical Investigation*.[122] Abstracts of the articles in this symposium of greatest interest to syphilotherapists appear in a recent issue [123] of the *American Journal of Syphilis, Gonorrhea and Venereal Diseases*.

120. Stocken, L. A., and Thompson, R. H. S.: British Anti-Lewisite: I. Arsenic Derivatives of Thiol Proteins, Biochem. J. **40**:529, 1946; II. Dithiol Compounds as Antidotes for Arsenic, ibid. **40**:535, 1946; III. Arsenic and Thiol Excretion in Animals After Treatment of Lewisite Burns, ibid. **40**:548, 1946.

121. Symposium on the Pharmacology of Dithiols, J. Pharmacol. & Exper. Therap. (supp.) **87**:1 (Aug.) 1946.

122. Symposium on Clinical Uses of 2,3-Dimercaptopropanol (BAL), J. Clin. Investigation **25**:451 (July) 1946.

123. Symposium on BAL, abstracted, Am. J. Syph., Gonor. & Ven. Dis. **31**: 93 (Jan.) 1947.

An excellent general review of the pharmacology and of the usefulness of 2,3-dimercaptopropanol in the therapy of heavy metal poisoning has been made by Brenton.[124]

2,3-Dimercaptopropanol in Arsenical Poisoning from Antisyphilitic Therapy.—The results of a cooperative study of the use of 2,3-dimercaptopanol (BAL) in the systemic treatment of arsenic poisoning have again been detailed by Eagle and Magnuson.[125] Their conclusions representing the results of therapy in 227 cases are of sufficient importance to be repeated here:

1. BAL dissolved in peanut oil with benzyl benzoate may be injected intramuscularly in man in individual doses of from 2.5 to 3 mg. per kilogram, repeated at four hour intervals. At higher dosages, an undue proportion of injections are followed by transient toxic reactions.

2. In fifty-five patients with arsenical encephalitis treated with BAL the overall mortality was 11 per cent. All fifteen patients with relatively mild cases recovered within one to four days. In severe cases, comatose or convulsing, the results varied with the time elapsed since the development of cerebral symptoms. Thus, the mortality in the first twenty-four severe patients (sic) treated with BAL from one-half to six hours after the development of symptoms was 20 per cent; while of nine patients in whom treatment was delayed for an average of thirty hours, five died. In general, the patients who recovered usually showed definite improvement in from one to two days and completely recovered in an average of four days.

3. In eighty-eight patients with arsenical dermatitis, of whom fifty-one had typical exfoliative cases, the administration of BAL usually stopped the progression of the inflammatory reaction and accelerated the healing process. The average time for definite improvement in the patients with severe cases successfully treated (80 per cent) was three days, and the average time for from 75 to 90 per cent recovery was thirteen days.

4. In ten of eleven patients with arsenical agranulocytosis the administration of BAL was followed by an increase in the total white blood cell count and an even more pronounced increase in the proportion and total number of polymorphonuclear leucocytes. The eleventh patient died.

5. In three of four patients who had in error received massive doses of arsenical (0.6, 0.4 and 0.6 Gm. mapharsen) the administration of BAL was followed by prompt symptomatic relief, and there were no late serious toxic complications. A fourth patient who received inadequate treatment with BAL after the single administration of 1.2 Gm. of mapharsen died on the seventh day.

6. In forty-four patients with a marked febrile reaction occurring as a complication of arsenotherapy, often associated with a toxic rash, the administration of BAL was usually followed by a drop in temperature and the disappearance of associated subjective symptoms. Thirty-six had completely recovered in

124. Brenton, H. L.: British Anti-Lewisite (BAL), J. Bowman Gray School Med. **5**:94 (May) 1947.

125. Eagle, H., and Magnuson, H. J.: The Systemic Treatment of Two Hundred and Twenty-Seven Cases of Arsenic Poisoning (Encephalitis, Dermatitis, Blood Dyscrasias, Jaundice, Fever) with 2,3-Dimercaptopropanol (BAL), Am. J. Syph., Gonor. & Ven. Dis. **30**:420 (Sept.) 1946.

from twenty-four to seventy-two hours, and all were well in eight days. Because this compilation is self-limited, it is difficult to assess the role of BAL.

7. In five of fourteen patients with so-called arsenical jaundice, the administration of BAL in relatively small doses was followed by symptomatic improvement. In three of those five patients this was shown to be associated with a prompt fall in the blood bilirubin level. In seven of the patients, however, there was either no effect or improvement was so slow that it could not be causally related to the BAL. The effect in the remaining two patients was debatable.

8. BAL had no therapeutic effect in three patients with aplastic anemia or in two patients with dermatoses following prolonged administration of Fowler's solution.

9. The administration of BAL was followed by an increased urinary excretion of arsenic in eleven patients with exfoliative dermatitis treated with BAL. The similar results in six normal subjects, and in twelve men given BAL from six to seventy-eight hours after the inhalation of minute amounts of an arsenical smoke, will be described in a later paper. The results in six patients with jaundice were, however, equivocal in that only two of the six showed a significantly increased excretion.

10. The dosage of BAL in the patients so far treated has averaged from 500 to 700 mg. in the first twenty-four hours and a total of from 1,000 to 1,500 mg. over a period of from three to seven days. In no patient has there been a serious systemic toxic reaction referable to BAL. In view of that fact, the encouraging therapeutic results obtained to date and the desirability of more intensive treatment, it is suggested that the unit dosage and the number of injections be increased in the serious manifestations of arsenical poisoning.

Toxicity of 2,3-Dimercaptopropanol.—The drug 2,3-dimercaptopropanol is itself toxic, but the margin of safety between the effective and the toxic level is large enough to make its use clinically feasible. Administered intramuscularly in peanut oil and benzyl benzoate, injections of 3 mg. per kilogram (average adult dose of 150 to 200 mg. or 1.5 to 2.0 cc. of a 10 per cent solution) may be repeated every four hours during the first forty-eight hours and once or twice daily thereafter until recovery is complete.

Cameron, Burgess and Trenwith [126] have sought by means of experiments on rabbits and rats to find out whether untoward effects may arise from the use of 2,3-dimercaptopropanol in conditions of impaired function of the kidneys and liver. Renal tubular damage was produced with uranium acetate, and carbon tetrachloride was used to damage the liver. When the drug was injected into animals with severe renal disease, no evidence of toxic effects greater than those in normal animals was obtained. With hepatic damage, however, there was enhanced toxicity. The authors suggest that care should be exercised when the drug is given to patients suspected of having impaired hepatic func-

126. Cameron, G. R.; Burgess, F., and Trenwith, V. S.: The Possibility of Toxic Effects from 2,3-Dimercaptopropanol in Conditions of Impaired Renal or Hepatic Function, Brit. J. Pharmacol. **2**:59 (March) 1947.

tion. They do not consider severe renal disease a contraindication to its use.

Friedham and Vogel [127] report experiments to show that the condensation product of a chemotherapeutically active arsenical with BAL may result in a new compound combining relatively low toxicity with significant spirochetocidal activity.

PENICILLIN: CHEMISTRY, PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

The Chemistry of Penicillin.—A brief history [128] of the extensive studies in the chemistry of penicillin carried out cooperatively by English and American investigators during World War II has recently been published. As a direct result of this enormous cooperative enterprise, the synthesis of penicillin was made possible. DuVigneaud and his fellow workers at Cornell [129] report the successful synthesis of benzyl penicillin in crystalline form by the condensation of *d*-penicillamine hydrochloride and 2-benzyl-4-methoxymethylene-5 (4)-oxazolone. These workers adduce evidence, utilizing many of the newer tools of chemical science, that their synthetic preparation is truly "penicillin." The melting point, ultraviolet and infra-red absorption spectrums, refractive indexes, antibiotic activity and specific rotation of the synthetic material were similar to those of natural benzyl penicillin. Of particular significance is the fact that the synthetic material was the same optical isomer as the natural product.

While the amounts of penicillin thus far synthesized are small, the importance of this accomplishment is that new preparations chemically related to penicillin now may be produced.

Penicillin Species.—There are marked discrepancies between the in vitro and the in vivo activity of penicillins G, F, X and K. This disparity is most striking with penicillin K, which is the most active of the four in vitro but the least effective in vivo, both in bacterial and in experimental syphilitic infections. Several groups have reported that penicillin K apparently disappears from the circulating blood of man with unusual rapidity. Since the urinary excretion of penicillin K was notably low in these experiments, it was presumed that some had been destroyed within the body.

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127. Friedham, E. A. H., and Vogel, H. J.: Trypanocidal and Spirochetocidal Compounds Derived from BAL and Organic Arsenicals, Proc. Soc. Exper. Biol. & Med. **64**:418 (April) 1947.

128. The Chemical Study of Penicillin: A Brief History, The Editorial Board of the Monograph on the Chemistry of Penicillin, Science **105**:653 (June 27) 1947.

129. Du Vigneaud, V.; Carpenter, F. H.; Holley, R. W.; Levermore, H. H., and Rachele, J. R.: Synthetic Penicillin, Science **104**:431 (Nov. 8) 1946.

Rotman-Kavka, Hirsh and Dowling,[130] in a comparative study of penicillins X and G and crystalline penicillin G, found that penicillin X achieves and maintains higher blood concentrations than similar amounts of penicillin G. Most of the bacteria tested were more sensitive to penicillin X than to penicillin G, but the difference was slight when the two were compared on a gravimetric basis.

The relative activities of the four penicillin species, G, F, X and K, vary, depending on the micro-organism against which they are tested. Eagle [131] found approximately a twofold difference in vitro between the least active and the most active of these four penicillins when tested against Staphylococcus aureus, group A hemolytic streptococcus and the nonpathogenic Reiter's strain of Spirochaeta pallida. The order of decreasing in vitro activity for these cultured spirochetes was $G > K > F = X$. The author points out that the same differences in the chemical configuration of the side group that determine the varying bactericidal activities of these penicillins may also variably affect the rate of their diffusion, excretion or inactivation in vivo and that their therapeutic activity was not necessarily parallel direct bactericidal action in vitro.

Discrepant reports concerning the effects of blood serum on the bactericidal activity of penicillin and the paradoxic finding that penicillin K is therapeutically almost inactive despite a high measure of bactericidal activity in vitro led Eagle [132] to study the susceptibility of various crystalline penicillins to inactivation by blood. Penicillins F, G, K and X were all found to be inactivated by human and rabbit serum. Two qualitatively different mechanisms apparently were involved: one, a slow inactivation of all four penicillins by a relatively thermostabile serum component; the other, a much faster inactivation observed only with penicillin K, due to a thermolabile factor in blood serum.

The urinary excretion of penicillin is so rapid that the slow destruction of penicillins F, G and X in the blood is of only secondary importance therapeutically. Nevertheless, it contributes to their rapid disappearance from the blood. The fact that penicillin X is inactivated more slowly than either F or G is reflected in blood levels which are higher and longer sustained than those afforded by the latter two species. Eagle [133] reports that both in man and in the rabbit penicillin

130. Rotman-Kavka, G.; Hirsch, H. L., and Dowling, H. F.: A Comparative Study of Penicillins X and G and Crystalline Penicillin G, New England J. Med. **236**:314 (Feb. 27) 1947.

131. Eagle, H.: The Relative Activity of Penicillins F, G, K and X Against Spirochetes and Streptococci in Vitro, J. Bact. **52**:81 (July) 1946.

132. Eagle, H.: The Inactivation of Penicillins F, G, K, and X by Human and Rabbit Serum, J. Exper. Med. **85**:141 (Feb. 1) 1947.

133. Eagle, H.: The Varying Blood Levels Afforded by Penicillin F, G, K, and X in Rabbits and Man, J. Exper. Med. **85**:163 (Feb. 1) 1947.

X provided higher and more sustained levels than did penicillins F and G similarly administered in equal dosage (0.6 mg. per kilogram) while penicillin K gave lower and more evanescent levels. The total amount of penicillins F, G and X recovered in the urine varied between 68 and 100 per cent, averaging 61, 87 and 74 per cent respectively in rabbits. In man, the amount of penicillins G and X recovered averaged 86 to 93 per cent respectively. In sharp contrast, the amount of penicillin K averaged 33 per cent in rabbits and 28 per cent in man. This suggests a rapid inactivation of penicillin K in vivo.

The therapeutic implications of these observations seem clear. By virtue of the higher and more sustained blood levels provided by penicillin X as compared with penicillins F or G, it is to be expected that the former would be more active in vivo than is indicated by its bactericidal activity in vitro relative to other penicillins. Penicillin K, on the other hand, because of its evanescent blood levels, should be far less active than its bactericidal activity in vitro would imply. Eagle [134] has demonstrated these facts in connection with type I pneumococci and Streptococcus pyogenes.

In contrast to these observations on penicillin K, Richardson and his co-workers [135] report that from a given plasma concentration the rate of disappearance of penicillin K is comparable to that of penicillin G. These investigators found in dogs that after the intravenous administration of penicillins G and K the latter was localized in the liver in higher concentrations than penicillin G. They further report that both penicillins appeared to be bound by plasma but that penicillin K was bound to a greater extent than penicillin G. Evidence is cited to suggest that the low recovery of penicillin K in plasma is not due to destruction of the penicillin and that alterations in renal excretion may be caused by its being bound by serum protein.

Tompsett, Schultz and McDermott [136] report that the antibacterial activities of penicillin species were antagonized by serum and by the albumin fraction of serum. The degrees of antagonism were quantitatively different for the several species, the extent of reduction in antibacterial activity being roughly proportional to the degree of binding of these substances as demonstrable by analysis. Moreover, the

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134. Eagle, H.: The Therapeutic Activity of Penicillins F, G, K, and X in Experimental Infections with Pneumococcus Type I and Streptococcus Pyogenes, J Exper. Med. **85**:175 (Feb. 1) 1947.

135. Richardson, A. P.; Miller, I.; Schumacher, C.; Jambor, W.; Pausy, F., and Lapedes, D.: Physiological Disposition of Penicillins G and K in Dogs, Proc. Soc. Exper. Biol. & Med. **63**:514 (Dec.) 1946.

136. Tompsett, R.; Schultz, S., and McDermott, W.: The Relation of Protein-Binding to the Pharmacology and Antibacterial Activity of Penicillins X, G, Dihydro F, and K, J. Bact. **53**:581 (March) 1947.

reduction in antibacterial activity was independent of any destruction of penicillin by the serum.

These data suggest that the antibacterial activity of the several penicillins is exerted only by the unbound portion of the drug and offer a possible explanation of the apparent discrepancies between the in vitro and the in vivo activity of the various penicillin species.

Tompsett, Schultz and McDermott [137] have further studied the absorption and excretion of penicillins X, G, dihydro F and K in human beings in an effort to evaluate the influence of the differences in the degrees of binding of these substances by serum protein. The duration of the serum concentrations afforded by all four penicillins after intramuscular injection of 300,000 units in human beings was uniform. Evidence is presented that previous findings of higher and more prolonged serum concentrations of penicillin X and lower, rapidly disappearing concentrations of penicillin K were artefacts created by differences in the antagonistic action of the serum on penicillin during the bioassay procedure. These differences in therapeutic effectiveness of the various penicillins could not be explained on the basis of differences in degree and duration of serum concentrations after equal doses.

Tepperman and his co-workers [138] have evidence that there is greater "inactivation" of penicillin K by the liver and kidneys than of penicillin G. It was found that penicillin levels in the blood were lower than usual in rabbits whose ureters had been ligated and still lower in animals that had been eviscerated and had had their kidneys ligated and that the lowering was greater with penicillin K than with penicillin G.

Penicillin Species in Syphilis.—With the identification and isolation of the several penicillin species, numerous attempts have been made to compare their relative effectiveness against the treponeme of syphilis. In man the ultimate comparison will require the treatment of many patients and the passage of many years. Meanwhile, the various penicillin species may be compared by any of several methods, the results of all of which are only suggestively applicable to the treatment of syphilis in man.

Olansky and Putnam [139] have tested the effectiveness of single doses of 50,000 units of two crystalline penicillins (G and X) as well as of

137. Tompsett, R.; Schultz, S., and McDermott, W.: Influence of Protein-Binding on the Interpretation of Penicillin Activity in Vivo, Proc. Soc. Exper. Biol. & Med. **65**:163 (June) 1947.

138. Tepperman, J.; Rakieten, N.; Valley, G., and Lyón, E. W.: Inactivation of Penicillin G and K by Liver and Kidney, Science **105**:18 (Jan. 3) 1947.

139. Olansky, S., and Putnam, L. E.: The Effect of the Sodium Salts of Crystalline Penicillin G, Crystalline Penicillin X, and Commercial Penicillins on Darkfield Positive Lesions of Syphilis, J. Ven. Dis. Inform. **27**:178 (July) 1946.

several commercial varieties on the rate of disappearance of spirochetes in dark-field-positive lesions of early syphilis. All types of penicillin tested had some spirocheticidal activity as demonstrated by the accelerated disappearance of surface treponemes. Crystalline penicillin G appeared at least as effective as any of several commercial penicillin preparations and penicillin X somewhat less effective than penicillin G.

Tucker and Robinson [140] have sought to determine a quantitative relationship between dosage (of penicillin G) and the disappearance time of surface Treponema pallida. These authors report the results of serial dark field studies of 35 patients with early syphilis. The sodium salt of penicillin G was administered on a gravimetric basis, and dark field examinations were performed at intervals of forty-eight hours. An inverse relationship between the dosage of penicillin G and the time required for disappearance of surface treponemes was demonstrated. Variability among patients receiving comparable dosages was, however, great enough to make the method unsatisfactory for the assay of penicillin preparations in man.

Methods of Administration.—Seeking information on the optimum time-dose relationships in the administration of sodium penicillin in the treatment of syphilis, Eagle, Magnuson and Fleischman [141] note that at least three variables may modify therepeutic efficacy, i. e., the number of injections, their frequency and the total amount of penicillin administered. The multiple permutations of these three variables have been studied in experimental syphilis in rabbits. The curative dose of penicillin sodium for syphilis in rabbits was found to be influenced to a striking degree by the number of injections. The greater the number, the less was the total amount of penicillin required for cure. On the other hand, provided the interval between injections was sufficiently long to avoid cumulative effects on the blood penicillin level (in which case therapeutic efficacy was paradoxically decreased) there appeared to be little difference whether penicillin was administered every four hours, twice daily or daily; an equal number of injections at a given dosage level produced comparable effects.

This extensive study is summarized by the authors as follows:

1. The therapeutic efficacy of sodium penicillin in experimental syphilis is profoundly modified by the method of its administration.

a. In rabbits injected at 4-hour intervals, as the number of injections was increased from 8 to 20 to 50, and the duration of treatment from 32 hours to

140. Tucker, H. A., and Robinson, R. C. V.: Disappearance Time of Treponema Pallidum from Lesions of Early Syphilis Following Administration of Crystalline Penicillin G, Bull. Johns Hopkins Hosp. **80**:169 (March) 1947.

141. Eagle, H.; Magnuson, H. J., and Fleischman, R.: The Effect of the Method of Administration on the Therapeutic Efficacy of Sodium Penicillin in Experimental Syphilis, Bull. Johns Hopkins Hosp. **79**:168 (Aug.) 1946.

8 days, the total curative dose (CD_{50}) fell from 80,000 to 1,600 to 360 units per kg., respectively. Similarly, in rabbits injected twice daily, merely doubling the number of injections from 8 to 16 and the duration of treatment from 4 days to 8 days reduced the total curative dose (CD_{50}) from 30,000 to 1,770 units per kg.

b. When the number of injections was kept constant, and only the interval between them varied, the curative dose was of the same order of magnitude whether injections were given every 4 hours, twice daily or daily (4,000, 1,770 and 4,000 units per kg.). On the other hand, when injections were given so frequently as to produce cumulative effects on the blood penicillin level, therapeutic efficacy was paradoxically reduced. Thus, the curative doses of sodium penicillin given in 16 injections at 4-hourly, 2-hourly and 1-hourly intervals were 4,000, 32,000 and more than 64,000 units per kg., respectively.

c. When the total duration of treatment was fixed, and the number of injections varied, the therapeutic efficacy of penicillin increased with the frequency of injection. In rabbits treated over a period of 4 days, as the frequency of injection was changed from once daily to twice daily to every four hours, and the number of injections correspondingly increased from 4 to 8 to 20, the total curative dose (CD_{50}) fell from 50,000 to 20,000 to 1,600 units/kg.

2. Although the therapeutic action of penicillin clearly involves both the tissue concentrations and the time over which they act, the latter time factor is by far the most important. Low concentrations acting over a long period of time (i. e., many small injections) were more effective than high concentrations acting over a short period (i. e., a few large injections to the same total dose). Within the time limits of the present experiments, the interval between injections was immaterial, provided they were not given too often: for an equal number of injections, treatment once daily was as effective as injections every 4 hours, with a suggestion of an optimum interval of 8 to 12 hours.

3. On the basis of the present experimental data, it may be anticipated that the results in the treatment of human early syphilis with sodium penicillin could significantly be improved by (a) prolonging the duration of treatment, (b) increasing the frequency and number of injections, and (c) increasing the total dosage of penicillin. The relative importance of these three factors is discussed in the text. The use of a suspension of calcium penicillin in oil and beeswax, or the administration of penicillin in a continuous intravenous, intramuscular or subcutaneous drip, or any other procedure which delays the absorption and excretion of penicillin would have the same effect as increasing the frequency and number of injections.

4. There is reason to believe that the treatment of syphilis with sodium penicillin need not be carried out in hospitalized patients, but that it may be given on an ambulatory basis once or twice daily, without necessarily sacrificing therapeutic efficacy, provided only that the patient receives the requisite total number of injections. The use of calcium penicillin in oil and beeswax, or of similar devices to delay the absorption and excretion of penicillin, may permit treatment to be given as infrequently as twice weekly, and perhaps even irregularly within that time interval.

5. The total curative dose (CD_{50}) of penicillin on the best schedule here tested was 500 units/kg. or approximately 0.3 mg./kg. of penicillin G. Milligram for milligram, penicillin is therefore 10 to 20 times as effective as mapharsen in the treatment of rabbit syphilis. In the human infection, however, penicillin is apparently only 2 to 4 times as active as mapharsen, mg. for mg.

With either penicillin or mapharsen, rabbit syphilis is easier to cure than the human disease, requiring less than ¼ to ⅛ as much mapharsen, and less than 1/20 to 1/40 as much penicillin.

Eagle and his associates have also shown (to be referred to in the section on the prophylaxis of syphilis) that the curative dose of penicillin in rabbit syphilis is directly related to the size of the inoculum and the duration of infection.

Hoffman [142] has made a comparison between the intramuscular and subcutaneous methods of administering aqueous solutions of penicillin. Three purified preparations were used and plasma levels of penicillin determined at half an hour, two and one-half hours and three hours after a single injection. Three dosage levels were employed. There were no significant differences between the plasma levels of penicillin obtained after subcutaneous injection and those obtained after intramuscular administration. All three purified preparations, the amorphous and crystalline penicillin sodium and crystalline penicillin potassium, gave essentially the same results. With purified penicillin, there were practically no local reactions of the "bee sting" type, which are not uncommon with more impure preparations.

Experimental Therapeutics.—The experiments of Arnold, Mahoney and Cutler [143] indicate that rabbits with early syphilis that have been treated with amounts of penicillin sufficient to effect biologic "cure" (as adjudged by lymph node transfers four months after treatment) can be reinfected with a homologous strain within ten days after treatment is completed. These experiments are important in that they imply that "cure" may be effected during the actual period of treatment, since reinfection is successful while the healing chancre of the first infection is still present and (although these authors did not study the point) while reagin produced by the first infection is still present in the blood.

Fleming and Wolf [144] have assayed the therapeutic effectiveness of relatively crude commercial penicillin in early (six weeks' duration) and late (six months' duration) syphilis in rabbits. Their method of treatment, intramuscular injections of an aqueous solution every three hours for thirty-two injections, was the same for rabbits with early as for those with late syphilis. The total amount of penicillin required to "cure" 50 per cent of the test animals (as adjudged by negative lymph node transfers eight weeks after treatment, the inadequacy of which the authors themselves recognize) was lower in the group whose infec-

142. Hoffman, W. S.: Subcutaneous Versus Intramuscular Administration of Penicillin, J. Lab. & Clin. Med. **31**:1165 (Nov.) 1946.

143. Arnold, R. C.; Mahoney, J. F., and Cutler, J. C.: Reinfection in Experimental Syphilis in Rabbits Following Penicillin Therapy, Am. J. Syph., Gonor. & Ven. Dis. **31**:264 (May) 1947.

144. Fleming, W. L., and Wolf, M. H.: The Therapeutic Effectiveness of Relatively Crude Commercial Penicillin in Early and Late Rabbit Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **30**:468 (Sept.) 1946.

tion was of longer duration (in early syyphilis the CD_{50} was 1,000 units per kilogram and in late syphilis approximately 500 units per kilogram). The occurrence of keratitis in 2 test animals whose lymph nodes had proved noninfectious causes the authors to question the validity of node transfer as a "test of cure."

Resistance to Penicillin.—From a study in which sixteen strains of bacteria were made resistant to penicillin G or penicillin X by serial passages in mediums containing increasingly larger amounts of these fractions, Dowling, Hirsh and O'Neil [145] conclude that "organisms which cause human infections usually do not show great differences in their relative sensitivity to penicillin G and penicillin X. In most instances, when resistance to one of these fractions increases, resistance to the other will also increase." In 2 patients with bacterial endocarditis the organisms responsible for the infection developed resistance to both penicillin fractions simultaneously.

In experiments designed to cast light on the question of whether T. pallidum may acquire tolerance to penicillin, Kolmer and Rule [146] found that in a small series of animals the Nichols-Hough strain of T. pallidum showed no evidence of acquired resistance to penicillin after three consecutive passages through the testes of rabbits treated with subcurative amounts of the drug.

Resistance to penicillin thus far has been no great problem in the treatment of syphilis. The possibility that penicillin-resistant strains eventually may develop, however, has not been overlooked. Nor is it unlikely that there may be developed, perhaps in the none too distant future, new antibiotic preparations therapeutically more effective against T. pallidum than penicillin.

A study by Sullivan, Stahly and Birkland [147] is of interest in this connection. These investigators studied reciprocal sensitivities to penicillin, streptomycin and streptothricin of strains of Staph. aureus which had been made resistant in vitro to each of these three antibiotic substances. The development of maximal resistance was accomplished after twelve transfers for streptomycin, twenty-five transfers for streptothricin and thirty-two transfers for penicillin. The principal purpose was to determine whether the development of resistance to one of the

145. Dowling, H. G.; Hirsh, H. L., and O'Neil, C. B.: Studies on Bacteria Developing Resistance to Penicillin Fractions X and G in Vitro and in Patients Under Treatment for Bacterial Endocarditis, J. Clin. Investigation **25**:655 (Sept.) 1946.

146. Kolmer, J. A., and Rule, A. M.: Acquired Resistance of Treponema Pallidum to Penicillin, Proc. Soc. Exper. Biol. & Med. **63**:240 (Nov.) 1946.

147. Sullivan, M.; Stahly, G. L., and Birkland, J. M.: Reciprocal Sensitivities of Staphylococcus Aureus to Streptomycin, Streptothricin and Penicillin, Science **104**:397 (Oct. 25) 1946.

antibiotic agents would result in resistance to one or both of the others. It was found that the strains which were resistant to streptothricin also were more resistant to streptomycin than were those in the parent culture but that the reverse of this was not true. With this one exception the development of resistance to one antibiotic agent did not result in increased resistance to either of the others.

Effect of Hyperpyrexia on Activity of Penicillin.—Having previously demonstrated [148] that the rate at which cultured spirochetes (Reiter) are killed in vitro increases with elevations in temperature, Eagle and his co-workers [149] have confirmed this observation in vivo against pathogenic strains of T. pallidum. When penicillin was injected intramuscularly in syphilitic rabbits every two hours for sixteen injections, it required 30,000 to 60,000 units per kilogram to cure 50 per cent and 90 per cent of the rabbits respectively. When the body temperature of rabbits during the period of administration of penicillin was increased by approximately 3 to 4 degrees over an average ten hour period, the total curative dose for 50 per cent of the animals fell to 3,000 and 8,000 units per kilogram. The authors consider that the favorable effect of fever on the therapeutic activity of penicillin in early syphilis at least in part reflects an enhanced spirocheticidal action of penicillin at higher temperatures, but they point out that fever may have a spirocheticidal effect of its own additive or synergistic to that of penicillin.

PROLONGATION OF ACTION OF PENICILLIN

One of the major disadvantages of penicillin as a therapeutic agent is the rapidity with which it is excreted in the urine. Relatively large doses must be given every few hours if detectable plasma concentrations are to be maintained. Many attempts have been made to prolong the therapeutic activity of penicillin. These attempts have in general been calculated either to delay the absorption of the drug or to decrease its renal excretion.

Delayed Absorption of Penicillin.—By far the most satisfactory method of delaying absorption after parenteral injection is the administration of penicillin in peanut oil and beeswax (Romansky and Rittman [150]).

A preliminary report of studies to determine the most satisfactory diluent for penicillin from the standpoint of maintaining satisfactory

148. Eagle, H., and Musselman, A. D.: The Spirocheticidal Action of Penicillin in Vitro and Its Temperature Coefficient, J. Exper. Med. **80**:493, 1944.

149. Eagle, H.; Magnuson, H. J., and Fleischman, R.: The Effect of Hyperpyrexia on the Therapeutic Efficacy of Penicillin in Experimental Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **31**:239 (May) 1947.

150. Romansky, M. J., and Rittman, G. E.: Penicillin Blood Levels for Twenty-Four Hours Following a Single Intramuscular Injection of Calcium Penicillin in Beeswax and Peanut Oil, New England J. Med. **233**:577 (Nov. 15) 1945.

blood levels for twenty-four hours has been made by Cannon, Lindstrom and Ospeck.[151] These authors' experiments with various oily diluents for penicillin indicate that of the oils tested peanut oil with a 4.8 per cent mixture of beeswax and hydrogenated cottonseed oil (melting point, 40 C.) produced the most satisfactory prolongation of the penicillin action. Increase of the dosage of penicillin at each injection not only heightened the level of penicillin in the blood but also prolonged (slightly) the duration of its action.

Incorporation of penicillin in vehicles of the water in oil type was found by Harris, Wilcox and Finland [152] to give only a slight and inconstant prolongation of penicillin levels in the blood.

There are technical difficulties in the administration of penicillin in a suspension of oil and 4.8 per cent beeswax. The preparation originally devised by Romansky and Rittman is in a solid state at room temperature and must be heated before injection is possible. A new preparation of unstated composition [153] that is fluid at room temperature is reported by Hirsh and his co-workers [154] to give prolonged penicillin levels in the blood, which, however, are somewhat inferior to those obtained with the original "Romansky formula."

Clinical Use of Penicillin-Oil-Beeswax.—Data from a study of 600 cases and from the clinical observation of 4,000 patients given 60,000 injections of penicillin calcium in beeswax and peanut oil are given in detail by Romansky.[155] The results in a variety of infections were "as satisfactory as those obtained by the multiple injections of penicillin in aqueous solution." The incidence of allergic reactions (urticaria and angioneurotic edema) after intramuscular injections of penicillin-oil-beeswax was approximately 5 per cent. Local reactions at the site of injection occurred, but they were more frequent when the preparation was given subcutaneously. The author was able to demonstrate that penicillin calcium in beeswax and peanut oil showed no loss of potency at room temperature for at least one year. At 37 C. potency was maintained for about nine months.

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151. Cannon, A. B.; Lindstrom, K., and Ospeck, A. G.: Maintenance of Penicillin Blood Levels After a Single Intramuscular Injection of Penicillin in Various Oils, Science **104**:414 (Nov. 1) 1946.

152. Harris, H. W.; Wilcox, C., and Finland, M.: Plasma Levels After Repository Injections of Penicillin in Water-in-Oil Emulsions, Proc. Soc. Exper. Biol. & Med. **63**:199 (Oct.) 1946.

153. Obtained from Merck & Co., Inc., Rahway, N. J.

154. Hirsh, H. L.; Dowling, H. F.; Vivino, J. J., and Rotman-Kavka, G.: Penicillin in Beeswax and Peanut Oil: A New Preparation Which Is Fluid at Room Temperature; Absorption and Therapeutic Use, J. Lab. & Clin. Med. **32**: 34 (Jan.) 1947.

155. Romansky, M. J.: The Current Status of Calcium Penicillin in Beeswax and Peanut Oil, Am. J. Med. **1**:395 (Oct.) 1946.

Penicillin-Oil-Beeswax in Experimental Syphilis.—The experiments of Eagle, Magnuson and Fleischman [156] establish the fact that in experimental syphilis in rabbits a single injection of penicillin in oil and beeswax is more effective therapeutically than a single injection of the aqueous solution and at least as effective as multiple small injections.

When an attempt was made to cure rabbits with early syphilis by a single massive injection, more than 600,000 units of an aqueous solution of penicillin per kilogram was required to cure one half of the animals, while with penicillin-oil-beeswax the CD_{50} was only 50,000 units per kilogram. As the total number of injections was increased, the relative advantage of the oil-beeswax preparation progressively diminished. To cure early rabbit syphilis in one day with a total of 50,000 units required one injection of the oil-beeswax preparation and twelve injections of the aqueous solution, to effect cure in four days with a total of 3,500 units per kilogram required four injections of oil-beeswax and sixteen of the aqueous solution and to cure in eight days with 800 units per kilogram required sixteen injections of the oil-beeswax preparation and thirty-two of the aqueous solution. Thus penicillin in aqueous solution had to be subdivided into two to fourteen times as many injections as the oil-beeswax suspension in order to be equally effective.

These experiments indicate a consistent superiority of penicillin in oil and beeswax over penicillin in aqueous solution. Unfortunately they were not carried out to their logical conclusion. With further subdivision of the doses of penicillin in aqueous solution it is entirely possible that the superiority of penicillin-oil-beeswax would be equaled and perhaps surpassed in therapeutic effectiveness by the aqueous solution.

Kolmer [157] has studied the therapeutic efficacy of penicillin in experimental early syphilis in rabbits and has compared its activity in isotonic solution of sodium chloride with that in suspension in peanut oil and beeswax. His results, unimpressive because of the small number of test animals used, suggest a unit for unit superiority of the peanut oil-beeswax suspension. In isotonic solution of sodium chloride the minimal single curative dose of penicillin by intramuscular injection was more than 100,000 units per kilogram of weight, whereas in oil-beeswax suspension it was approximately 40,000 units. Given twice

156. Eagle, H.; Magnuson, H. J., and Fleischman, R.: Observations on the Therapeutic Efficacy in Experimental Syphilis of Calcium Penicillin in Oil and Beeswax and Their Bearing on Its Use in Man, Am. J. Syph., Gonor. & Ven. Dis. **31**:247 (May) 1947.

157. Kolmer, J. A.: Penicillin in the Treatment of Experimental Syphilis of Rabbits: I. The Therapeutic Activity of Penicillin in Single and Multiple Doses in Isotonic Solution of Sodium Chloride and Peanut Oil-Beeswax by Intramuscular Injection, Arch. Dermat. & Syph. **55**:741 (June) 1947.

daily over a period of eight days, it was 16,000 units. The minimal curative dose of penicillin-oil-beeswax by intramuscular injection once a day for eight days was approximately 8,000 units; given twice daily, it was, paradoxically, 16,000 units.

Inhibitory Effect of Caronamide on Renal Excretion of Penicillin.—. Attempts have been made to decrease the renal excretion of penicillin by the administration of iodopyracet injection ("diodrast") and para-aminohippuric acid, but both of these substances must be given in large amounts by continuous intravenous infusion. A new approach to the problem of decreasing the urinary excretion of penicillin involves the use of a compound, 4'-carboxyphenylmethanesulfonanilide, called by Beyer [158] caronamide. Unlike "diodrast" and paraaminohippuric acid, which compete with penicillin on a mass action basis for transport through the renal tubules, caronamide does not appear to be excreted by the tubules but is believed to suppress penicillin excretion by blocking an enzyme system involved in the transport of penicillin through the tubular cells. The compound is rapidly absorbed from the gastroenteric tract and therefore may be given orally.

The oral administration of caronamide was found by Vermey and Miller [159] to enhance the therapeutic effectiveness of intramuscularly administered penicillin in mice experimentally infected with type I pneumococci or Eberthella typhosa. Since caronamide has no demonstrable bactericidal action of its own and does not enhance that of penicillin in vitro, it is believed that the increased effectiveness of penicillin results from the influence of caronamide on the duration and magnitude of blood and tissue levels of penicillin.

PENICILLIN IN THE TREATMENT OF SYPHILIS

Like many another new form of therapy, penicillin therapy of syphilis is progressing through the cycle of enthusiasm and reaction. The limitations of this form of therapy gradually are becoming apparent. Even the most skeptical observer no longer denies that penicillin is a valuable adjunct to syphilotherapy or that it is in some respects superior to any previous form of treatment. That it has serious drawbacks is recognized by its most ardent protagonists.

Until recently, the literature on the use of penicillin in syphilis has been confined almost exclusively to American and British journals. Within the past year, general discussions of the subject have become

158. Beyer, K. H.: New Concept of Competitive Inhibition of the Renal Tubular Excretion of Penicillin, Science **105**:94 (Jan. 24) 1947.

159. Vermey, W. F., and Miller, A. K.: Effect of Caronamide upon Penicillin Therapy of Experimental Pneumococcus and Typhoid Infections in Mice, Proc. Soc Exper. Biol. & Med. **65**:222 (June) 1947.

available in French,[160] Spanish,[161] Dutch [162] and German [163] publications. Recent American summations include those of O'Leary and Kierland [164] and Reynolds.[165]

Penicillin in Early Syphilis.—Moore [5] in his monograph on penicillin in syphilis makes the following suggestions for the use of commercial penicillin in early syphilis:

1. When sodium penicillin in aqueous solution is used for the treatment of syphilis in man, injections should be given by the intramuscular route every 2-4 hours, preferably every 2-3 hours day and night around the clock, for a minimum of 7½-8 days.

The minimum dose of previously produced and presently available commercial penicillin should be, *for seronegative primary syphilis,* not less than 3.6 million units (90 injections of 40,000 units each, given every 2 hours; or 60 injections of 60,000 units each, given every 3 hours); *for seropositive primary* and *early secondary syphilis,* not less than 5.4 million units (90 injections of 60,000 units each or 60 injections of 90,000 units each).

For a first relapse (including reinfection, infectious or serologic relapse) of early syphilis after previous treatment of early syphilis, the above course should be repeated; *plus* 360 mgm. mapharsen (or an analogue) given twice to three times weekly in 6 individual intravenous injections of 60 mgm. each; *plus* 1,200 mgm. bismuth subsalicylate, given twice weekly in 6 individual intramuscular injections of 0.2 gm. each.

For a second relapse of early syphilis after previous penicillin treatment, the patient should be transferred from penicillin entirely and placed on metal chemotherapy with arsenic and bismuth, preferably by the 26 week schedule employed by the Army and Navy (40 intravenous injections of mapharsen, or an analogue, 16 intramuscular injections of bismuth subsalicylate).

2. The only presently satisfactory method of absorption delaying of penicillin is the administration of calcium penicillin in peanut oil-beeswax. Detailed information is not yet available as to the effects of this preparation in large series of patients with early syphilis, or with any other stage of the disease. It is known, however, that a single intramuscular injection of 600,000 units will produce a therapeutically active blood level for from 20-28 hours. If calcium penicillin in peanut oil-beeswax is used in any stage of syphilitic infection, the average

160. Bouvier, J. B.: La pénicilline dans la traitement de la syphilis, Paris méd. **36**:554 (Dec. 14) 1946. Pautrier, L. M.: Quelle place la pénicilline peut-elle prendre à l'heure actuelle dans le traitement de la syphilis, Presse méd. **55**:187 (March 19) 1947.

161. Spilzinger, C.; Gunche, F. F., and Bigatti, A.: Penicilina y sífilis, Rev. Asoc. méd. argent. **61**:3 (Jan.-Feb.) 1947. Reynolds, F. W., and Pardo, O. A.: La penicilina en el tratamiento de sifilis precoz, Am. clinica **10**:314 (April) 1947.

162. de Bergh, J.: Over de behandeling van syphilis met penicilline, Nederl. tijdschr. v. geneesk. **90**:1672 (Nov. 16) 1946.

163. Bohnstedt, R. M.: Behandlung der Syphilis mit Penicillin, Ztschr. f. Haut- u. Geschlechtskr. **12**:396 (June) 1947.

164. O'Leary, P. A., and Kierland, R. R.: Today's Treatment of Syphilis, J. A. M. A. **132**:430 (Oct. 26) 1946.

165. Reynolds, F. W.: Penicillin in the Treatment of Syphilis, Am. J. Med. **1**:661 (Dec.) 1946.

daily dose for an adult should be 2 cc. (600,000 units) and a total duration of treatment from 8-15 days or longer, depending on the stage of the infection. For early syphilis, a minimum total dose of 4.8 to 6.0 million units of this preparation is advised.

Calcium penicillin in peanut oil-beeswax should not be administered by the subcutaneous route, since under these circumstances the incidence of sensitizing reactions, with giant urticaria and angioneurotic edema, is excessively high.

3. There is evidence, both from the experimental laboratory and the clinic, that the addition of arsenic (mapharsen or its analogues) in subcurative dosage to a penicillin treatment schedule enhances the therapeutic effect of each drug. A suggested total dose of an arsenoxide for this purpose is 300-600 mgm., administered in divided intravenous injections of 40-60 mgm. each, over a total time period of 1-4 weeks.

It is recognized that the administration of arsenic in this dosage introduces a risk of serious reactions or death, in inverse proportion to the time interval of its administration. If 300-360 mgm. are given within 7-9 days, the expected mortality rate is approximately 1 : 3,000 to 1 : 4,000. If the same dosage is given over a total period of four weeks, this risk is reduced to about 1 : 30,000.

In view of this consideration, and of possible technical difficulties encountered in the administration of arsenic or in the mere prolongation of treatment necessitated thereby, opinion is divided as to the desirability of including this drug in a recommended penicillin treatment schedule. The majority opinion of a group of competent experts is that the results of penicillin alone, in the dosage and time recommended above, would be satisfactory in a sufficiently large proportion of patients with early syphilis treated for the first time to justify eliminating arsenic from the original course of treatment, reserving its use for relapsing cases.

4. There is both clinical and experimental evidence to indicate that an insoluble bismuth salt administered intramuscularly in an oil suspension, e. g., bismuth subsalicylate, produces a slowly absorbed bismuth depot which continually releases small amounts of therapeutically effective bismuth for a period of from 3 to 6 months. There is likewise evidence to indicate that bismuth added to arsenic materially improves the results of metal chemotherapy. If bismuth is added to a penicillin or penicillin-arsenic schedule for early syphilis, it may be anticipated that the incidence of infectious relapse within the first 6 to 12 months after treatment will be materially reduced. This is probably accomplished, for the first few months after treatment, by bismuth effect alone. Later relapse is perhaps prevented or minimized by the fact of development of the patient's own immunity. Whether or not bismuth is of value in effecting cure of the individual patient, it should nevertheless be of considerable aid in minimizing infectious relapse, and thereby reducing the risk of spread of infection.

If bismuth is employed, the individual dose should be 200 mgm. (0.2 gm.) (*expressed as the subsalicylate, not as bismuth metal*). A total of 1,000 mgm. (5 injections) given every other day for a total of 9 days is unlikely to produce stomatitis except in patients with extremely bad oral hygiene, or renal damage in patients with previously undamaged kidneys. If the total dose is larger than 1,000 mgm., injections should be given not oftener than twice weekly.

However, the opinion of a group of experts is also divided as to the desirability of including bismuth with the original course of penicillin in early syphilis. The majority believed, as for arsenic, that bismuth should be reserved for use in relapsing cases.

It should be emphasized that these suggestions for the use of penicillin in early syphilis represent a combination of medical desirability and expediency.

They are based on presently available information, are tentative only, and are subject to revision within the next few months as further information accumulates.

It is also most vigorously to be emphasized that in the adoption of penicillin therapy for syphilis, the eventual value of which will not be determined for several years to come, the physician has a particular responsibility for careful follow-up and frequently repeated post-treatment observation on all patients so treated.

There have been in progress in the United States two extensive studies of various penicillin schedules for the rapid treatment of early syphilis. The results obtained by the thirty-six clinics [166] cooperating with the Syphilis Study Section of the National Institute of Health have recently been summarized by Merrell.[167] Those reported by the Cooperating Rapid Treatment Facilities [168] of the United States Public Health Service have been published by Heller.[169] The most recent compilation is outlined in a progress report dated December 1946.[170] The results obtained by the Syphilis Study Section are expressed in terms of cumulative failure rates and those obtained by the rapid treatment centers in terms of cumulative retreatment rates (table 2).

From the extensive data of the Syphilis Study Section and the rapid treatment centers there are now emerging several facts regarding the use of penicillin in early syphilis:

1. Dosage. Total doses of penicillin amounting to 1,200,000, 2,400,000 and 4,800,000 units are of about the same therapeutic effectiveness (fig. 1). With smaller total doses (300,000 and 600,000 units) there is an even greater percentage of treatment failures.

2. Interval between injections. There are no apparent differences between schedules of therapy in which the injections of aqueous solution of penicillin are given every two hours, every three hours or every six hours (fig. 2).

3. Duration of treatment. When other variables in the treatment schedule are held constant and only the duration of treatment varied,

166. Several of the clinics (Bauer and others: Am. J. Syph., Gonor. & Ven. Dis. **31**:45 [Jan.] 1947; Bundesen and others: ibid. **30**:475 [Sept.] 1946; Smith and others: Arch. Dermat. & Syph. **55**:644 [May] 1947) have reported their results separately and in detail. Since all the material is incorporated in the data of the Central Statistical Unit, these articles are not reviewed.

167. Merrell, M.: Results of the Nation-Wide Study of Early Syphilis (available in mimeographed form).

168. At least two rapid treatment centers (Leavitt, H. M.: Am. J. Syph., Gonor. & Ven. Dis. **31**:27 [Jan.] 1947; Holley, H. L.: ibid. **31**:41 [Jan.] 1947) have reported their data separately.

169. Heller, J. R., Jr.: Results of Rapid Treatment of Early Syphilis, J. Ven. Dis. Inform. **27**:217 (Sept.) 1946; Results of Rapid Treatment of Early Syphilis, J. A. M. A. **132**:258 (Oct. 5) 1946.

170. Rapid Treatment of Early Syphilis: Progress Report, Cooperating Rapid Treatment Facilities and U. S. Public Health Service, Venereal Disease Division, December 1946.

TABLE 2.—*Results Twelve to Fifteen Months After Treatment for Secondary Syphilis in Rapid Treatment Centers*

Schedule of Therapy	Total Patients Observed for 12 to 15 Months	Cumulative Percentage Retreated	Patients with Clinically Negative Reactions			
			Seropositive		Seronegative	
			No.	%	No.	%
Penicillin only						
600,000 units, 10,000 every 3 hr.....	197	32.9	25	12.7	107	54.3
1,200,000 units, 20,000 every 3 hr.....	131	26.5	14	10.7	82	62.8
1,200,000 units, 40,000 every 3 hr.....	247	21.0	42	17.0	153	62.0
1,200,000 units, 40,000 every 6 hr.....	319	22.7	63	19.8	188	57.4
1,500,000 units, 20,000 every 2 hr.....	28	22.4	5	17.6	17	59.9
1,600,000 units, 20,000 every 3 hr.....	189	20.8	47	24.9	102	54.1
1,700,000 units, 20,000 every 2 hr.....	45	21.3	9	20.2	26	58.4
2,400,000 units, 40,000 every 3 hr.....	247	21.0	42	17.0	153	62.0
2,400,000 units, 80,000 every 3 hr.....	171	21.1	29	16.9	106	61.9
Penicillin (peanut oil and beeswax)						
4,800,000 units, 300,000 every 12 hr.....	38	13.1	6	15.8	27	71.0
4,800,000 units, 600,000 every 24 hr.....	39	18.2	7	15.1	31	66.8
Penicillin and oxophenarsine hydrochloride						
300,000 units, 5,000 every 3 hr.; 320 mg. of oxophenarsine hydrochloride, 40 mg. each day "8-3-0".....	41	29.6	8	19.4	21	51.0
1,200,000 units, 20,000 every 3 hr.; 320 mg. of oxophenarsine hydrochloride 40 mg. each day "8-12-0".....	415	16.6	65	15.7	281	67.7
1,200,000 units, 16,667 every 3 hr.; 1 mg. per kilogram (maximum, 60 mg. of oxophenarsine hydrochloride on 1st, 3d, 5th, 7th and 9th days) "5-12-0"....	221	16.9	56	25.3	128	57.8
Penicillin, oxophenarsine hydrochloride and bismuth						
600,000 units, 10,000 every 3 hr.; 1 mg. per kilogram (maximum, 60 mg. of oxophenarsine hydrochloride on each of 8 days); 200 mg. of bismuth on 1st, 5th and 8th day "8-6-3".....	787	18.4	210	26.7	432	56.9
1,200,000 units, 16,667 every 3 hr.; 1 mg. per kilogram (maximum, 60 mg. of oxophenarsine hydrochloride on 1st, 3d, 5th, 7th and 9th day); 200 mg. of bismuth on 1st, 5th and 9th day "5-12-3"	632	15.1	201	31.8	336	53.1
Penicillin and fever therapy						
600,000 units in 42 hours; 8 to 10 hours of fever sustained at 104 to 106 F....	47	44.1	6	12.9	20	42.9
1,200,000 units in 29½ hours; 6 hours of fever sustained at 106 F.....	80	26.1	9	11.3	50	62.6
1,200,000 units, 20,000 every 3 hr.; 3 sessions of fever of 3 hours each.....	36	14.2	1	2.8	30	83.2
One day fever therapy — temperature maintained at 105 to 106 F. for 6 to 8 hours; 150 mg. of bismuth; 1.7 or more mg. per kilogram of oxophenarsine hydrochloride (or total of 120 mg.)	349	23.2	37	10.6	231	66.3
Five day intravenous drip—1,200 mg. of oxophenarsine hydrochloride.....	130	11.1	25	19.2	91	69.7
Eight day intravenous drip—1,080 to 1,200 mg. of oxophenarsine hydrochloride and 12 injections of bismuth.....	231	11.1	50	21.7	155	67.2
Schoch (11 to 20 days)—1,200 or more mg. of oxophenarsine hydrochloride and varying amounts of bismuth.....	105	15.4	29	27.6	60	57.0

it appears to make little difference whether penicillin is given over a period of four days, seven and a half days or fifteen days (fig. 3).

4. Stage of the disease. From all available reports it is apparent that the results of penicillin therapy are significantly more satisfactory when treatment is started early in the course of the disease. Nowhere is this more strikingly illustrated than in the results of penicillin therapy in the Army.

Sternberg and Leifer [171] have analyzed the Army records of 1,400 soldiers with early syphilis treated with 2,400,000 units of penicillin in

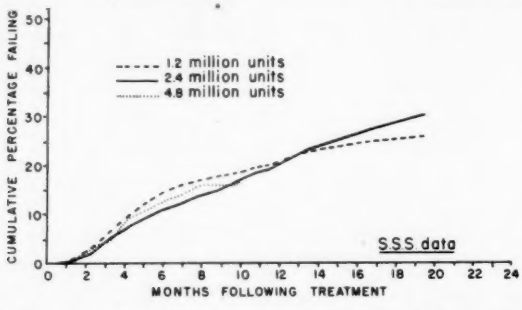

Fig. 1.—Cumulative failure rates by total dosage of penicillin—penicillin alone, administered in divided doses every three hours for seven and one-half days.

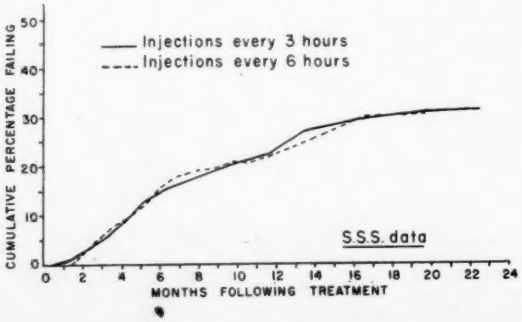

Fig. 2.—Cumulative failure rates by time interval between injections of penicillin—penicillin alone, 1,200,000 units over a period of four days.

aqueous solution given in divided doses over a period of seven and one-half days. There were no severe toxic reactions, and all patients completed the prescribed course of treatment. Satisfactory progress was observed in 94.3 per cent of 600 cases of seronegative primary

171. Sternberg, T. H., and Leifer, W.: Treatment of Early Syphilis with Penicillin, J. A. M. A. **133**:1 (Jan. 4) 1947.

syphilis, in 89.9 per cent of 564 cases of seropositive primary syphilis and in 83.0 per cent of 236 cases of secondary syphilis. The cerebrospinal fluid of 719 patients was examined after therapy. It was normal in 714 and abnormal in 5 (0.69 per cent). The high over-all satisfactory progress rate (90.6 per cent), admittedly tentative because of inadequate follow-up, was attributed to the considerable proportion of cases in which the disease was in the primary stage (83.1 per cent) and to the fact that the patients probably received penicillin of satisfactory potency. There were 40 for whom the treatment failed (5 per cent) among the 790 white patients, as contrasted with 92 (15 per cent) among the 610 Negro patients. The implications of the disparity with respect to race are thought possibly to involve a higher incidence of reinfection among the Negro troops. Reinfection might be expected to occur more frequently in the Negro groups since the incidence of

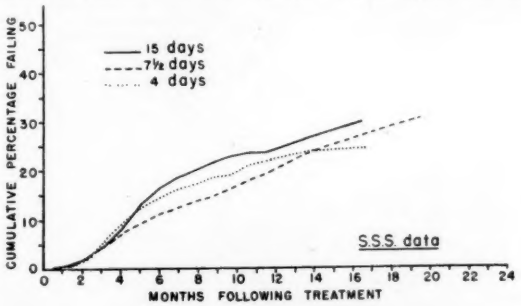

Fig. 3.—Cumulative failure rates by duration of therapy—penicillin alone, 2,400,000 units in injections given every three hours.

syphilis among them was consistently twelve to fifteen times that among the white troops.

5. Aqueous solution of penicillin versus penicillin-oil-beeswax. The therapeutic results with penicillin in oil and beeswax are at least as good as those with any schedule involving aqueous solutions of penicillin.

Favorable results in small series of patients treated with penicillin in oil and beeswax have been reported by Koch [172] and by Romansky and Rein.[173] Thomas, Landy and Cooper [174] have treated, with "unusually satisfactory" results, 802 patients with primary or secondary syphilis

172. Koch, R. A.: Ambulatory Intensive Treatment of Syphilis with Calcium Penicillin in Oil and Wax, Urol. & Cutan. Rev. **50**:461 (Aug.) 1946

173. Romansky, M. J., and Rein, C. R.: Treatment of Early Syphilis with Calcium Penicillin-Oil-Beeswax, J. A. M. A. **132**:847 (Dec. 7) 1946.

174. Thomas, E. W.; Landy, S., and Cooper, C.: Rapid Treatment of Early Syphilis with Penicillin in Beeswax and Oil, J. Ven. Dis. Inform. **28**:19 (Feb.) 1947.

with 4,800,000 units of penicillin in beeswax and peanut oil given over a period of eight days. Two treatment schedules were utilized: one group received two injections of 300,000 units daily; the other, one injection of 600,000 units daily. In their experience there appeared to be no advantage in giving more than one daily injection of penicillin-oil-beeswax. They attribute approximately 40 per cent of their treatment failures to reinfection rather than to relapse.

6. Penicillin alone versus penicillin combined with metal chemotherapy or fever therapy. Since the demonstration of Eagle and his co-workers [175] of a synergistic action between penicillin and oxophenarsine hydrochloride in experimental rabbit syphilis, many different schedules combining penicillin and heavy metals have been used in man.

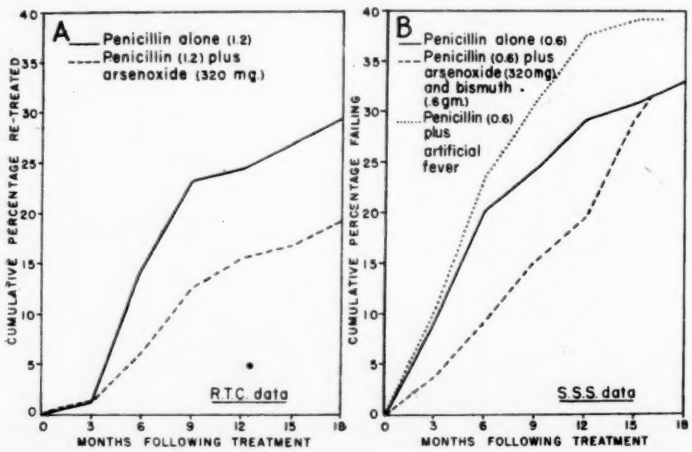

Fig. 4.—Comparison between penicillin alone and penicillin plus metal chemotherapy or fever therapy. *A*, cumulative percentage of patients retreated (data from rapid treatment centers); *B*, cumulative failure rates (Syphilis Study Section data).

The reports currently available are discrepant. The data from the rapid treatment centers suggest that the addition of oxophenarsine hydrochloride to aqueous solution of penicillin significantly reduces the percentage of patients who have to be retreated (fig. 4 *A*). Superiority of the combined penicillin oxophenarsine hydrochloride also was apparent early in the course of the work of the Syphilis Study Section, but with more prolonged follow-up observation the advantage was not maintained (fig. 4 *B*).

From neither study does there appear to be any virtue in short term courses of penicillin used in conjunction with artificial fever therapy,

175. Eagle, H.; Magnuson, H. J., and Fleischman, R.: The Synergistic Action of Penicillin and Mapharsen (Oxophenarsine Hydrochloride) in the Treatment of Experimental Syphilis, J. Ven. Dis. Inform. **27**:3 (Jan.) 1946.

despite Eagle, Magnuson and Fleischman's report [176] that in experimental rabbit syphilis there is a significant increase in the therapeutic efficacy of penicillin at fever temperatures.

7. Types of failure. In the data of the Syphilis Study Section the treatment failures are separated into three groups according to the ascribed cause of failure: (1) clinical relapse; (2) serologic relapse or seroresistance, and (3) probable reinfections (a "consensus of opinion" classification that lacks objectivity).

There were no great differences among the various schedules of treatment with respect to the incidence of clinical relapses, which at seventeen months varied from about 3 to 7 per cent. The distribution of treatment failures was, in general, approximately that shown in figure 5.

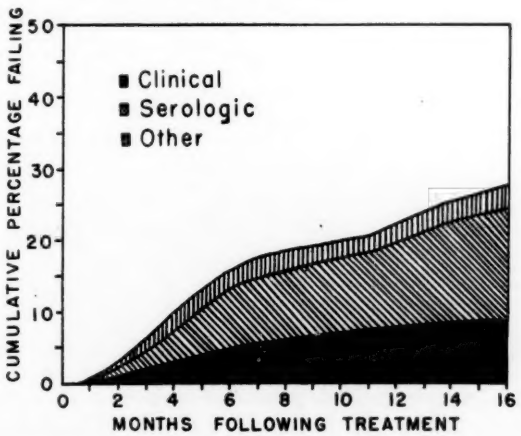

Fig. 5.—Cumulative failure rates by types of failure—penicillin alone, 1,200,000 units.

8. Reactions to rapid therapy. Throughout all the reports, the relative safety of schedules using penicillin alone as compared with schedules combining oxophenarsine hydrochloride with penicillin is apparent. In the experiences of the cooperating rapid treatment centers, there were no fatalities when penicillin was used without other drugs. The rate of severe reactions per thousand patients treated was only 8.6 for penicillin sodium alone and 5.1 for penicillin-oil-beeswax (table 3.)

A total of 11 deaths from treatment occurred when oxophenarsine hydrochloride was used concurrently with penicillin: the rate was 1 death for every 5,700 patients treated with this drug in combination

176. Eagle, H.; Magnuson, H. J., and Fleischman, R.: The Effect of Hyperpyrexia in the Therapeutic Efficacy of Penicillin in Experimental Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **31**:239 (May) 1947.

with penicillin sodium and 1 death for every 12,400 patients given it with penicillin-oil-beeswax. Hemorrhagic encephalitis was the principal cause of death.

Some French syphilotherapists have long divided the treatment of early syphilis into two phases: a "treatment of attack" and a "treatment of consolidation." Several have recently endorsed the use of penicillin as a satisfactory method of attack, but they are for the most part reluctant to dispense with follow-up metal chemotherapy to consolidate the early spirocheticidal effects of penicillin. The recently expressed ideas of Huriez and Desurmont [177] and of Barker Beeson [178] are an example of this.

Merklen and Vermeil [179] suggest that it is illogical to use penicillin alone in early syphilis. They recommend that antisyphilitic therapy be started with penicillin because of its prompt treponemicidal action and

TABLE 3.—*Severe Reactions and Deaths Reported by Thirty-Six Rapid Treatment Centers from July 1946 Through March 1947*

Type of Treatment	Total Patients Treated	Severe Reactions		Number of Deaths from Treatment
		No.	Rate per Thousand	
Aqueous solution of penicillin	12,157	104	8.6	0
Penicillin-oil-beeswax	4,106	21	5.1	0
Aqueous solution of penicillin with oxophenarsine hydrochloride	57,200	912	15.9	10
Penicillin-oil-beeswax with oxophenarsine hydrochloride	12,425	167	13.4	1
Total	85,888	1,204	14.0	11

because of its curative action against concomitant gonococcic infections and that this be followed by the use of arsenicals and bismuth. Having employed this schedule of therapy in a limited number of patients, Merklen and Nezelof [180] report that their early results have been entirely satisfactory.

In a small series of 17 patients Levaditi and Vaisman [181] found a combination of penicillin and bismuth a satisfactory treatment of early

177. Huriez, C., and Desurmont, M.: Les pénicillo-chimothérapies d'assaut de la syphilis récente, Presse méd. **35**:401 (June 14) 1947.

178. Barker Beeson, M. B.: La penicilline dans le traitement de la syphilis, Ann. de dermat. et syph. **8**:395 (July-Aug.) 1946.

179. Merklen, F. P., and Vermeil, G.: Traitement antisyphilitique d'attaque et de blanchiment rapide pénicillino-arsenical, Paris méd. **37**:54 (Feb. 1) 1947.

180. Merklen, F. P., and Nezelof, C.: Essai de traitement accéléré de la syphilis: Assaut massif arsenico-bismuthique associé a des doses reduites de pénicilline, Paris méd. **37**:119 (March 8) 1947.

181. Levaditi, C., and Vaisman, A.: Traitement de la syphilis par une association liposoluble de bismuth et d'ester méthylique de pénicilline, Presse méd. **57**: 781 (Nov. 23) 1946.

syphilis and one free from the undesirable reactions of arsenotherapy. They believe that this form of therapy combines the treponemicidal action of penicillin with a desirable prolonged suppressive effect from bismuth.

Hazel [182] has employed a treatment schedule in a small series of patients with early syphilis of ten daily injections of penicillin-oil-beeswax administered concomitantly with oxophenarsine hydrochloride every other day. After the completion of this intensive treatment the administration of the arsenical was continued once weekly until a total of twenty injections had been given; treatment was then concluded with five weekly injections of bismuth subtartrate. Schedules of this type are adaptable to office practice. Judging from this author's early experience, they would appear to be highly efficacious.

The Serologic Response Following Penicillin Therapy.—Data comparing the serologic response following penicillin therapy with that following previously established methods of treatment have been presented by Clark, Maxwell and Scott.[183] The effects of age, sex, race, duration of infection and asymptomatic neurosyphilis on serologic responses are considered. The serologic changes observed during the first eight weeks after penicillin therapy for early syphilis were comparable to those obtained during weekly treatment with arsenical drugs, although with infections of longer duration there was apparently some retardation in the rate of fall of serum reagin after the use of penicillin. A linear relationship between duration of infection and rate of fall of reagin was shown. A study of the serologic response in terms of age, race and sex demonstrated in this material a delayed serologic response in Negro females and in patients under 20 years of age. Evidence is presented that the retarded response observed in these groups is related to the higher percentage of patients who had (*a*) longer duration of disease, (*b*) less efficacious treatment schedules or (*c*) a high incidence of recurrent lesions or to a combination of these factors.

The serologic response of the blood appeared to be independent of the presence or absence of abnormalities in the cerebrospinal fluid. The importance of the several factors which influence results in comparative serologic studies of this kind is discussed. These include: (1) the statistical method of analysis; (2) variations in sensitivity of the serologic tests used, and (3) differences in methods of reporting quantitative results and in defining the end point in quantitative technics.

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182. Hazel, O. G.: Considerations with Respect to the Application in Private Practice of Penicillin Therapy for Early Syphilis, J. Ven. Dis. Inform. **28**:103 (June) 1947.

183. Clark, E. G.; Maxwell, R. W., and Scott, V.: The Serologic Response Following Penicillin Therapy for Early Syphilis, Am. J. M. Sc. **213**:535 (May) 1947.

Maillard and Orzel [184] have employed quantitative complement fixation tests in the study of 693 patients with early syphilis who received treatment with penicillin. These authors, finding significantly higher titers in patients with secondary syphilis than in those in the primary stage of the disease, express their belief that quantitative tests are of considerable value in estimating the probable duration of a recently acquired infection. They stress the even greater value of quantitative serologic tests in determining the effectiveness of treatment of early syphilis, noting that in their group of patients serologic relapse usually coincided with the reappearance of infectious mucocutaneous lesions.

Heggie and his co-workers [185] believe that flocculation tests and complement fixation tests should be performed routinely in parallel, and they emphasize the fact that since the introduction of penicillin therapy this routine parallel testing is more than ever necessary. If only one test can be undertaken, then it is believed that a flocculation test should be used.

Thomas [186] has recorded certain observations on the clinical significance of quantitative serologic tests for syphilis. He believes that "patients with negative spinal fluid findings but persistently low blood STS titers of less than 10 (units) for more than one year after rapid treatment for primary or secondary syphilis require no further therapy unless marked rises in STS titer occur." Patients treated for primary or secondary syphilis who continue to have positive reactions to serologic tests in high titer should in his opinion be retreated, but he cautions that the physician should not expect rapid drops in the titers of such patients after retreatment. Most patients given rapid treatment for early latent syphilis of less than six months' duration became seronegative within one year after treatment. The persistence of low titers in such patients for more than one year is not, he thinks, an indication for further treatment. The longer the duration of the latent syphilitic infection, the longer was the time required for the reactions to blood tests to become negative. The aim of treatment in late latent or late symptomatic syphilis is primarily to prevent further progress of the disease. Thomas expresses the belief that if notable sustained rises in titer occur further treatment is indicated but that patients who

184. Maillard, E. R., and Orzel, A.: The Value of the Quantitatively Standardized Complement Fixation Test in the Diagnosis and Treatment of Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **30**:490 (Sept.) 1946.

185. Heggie, J. F.; Maguire, J. C.; Bull, M. M., and Heggie, R. M.: Results of Parallel Kahn and Wassermann Tests in Relation to Penicillin Therapy of Syphilis, Lancet **1**:588 (May 3) 1947.

186. Thomas, E. W.: The Clinical Significance of the Quantitative Serologic Tests for Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **30**:317 (July) 1946.

continue to have gradually decreasing titers over years require no treatment.

Penicillin in Late Syphilis.—Penicillin in Benign Late Syphilis: That visceal (hepatic) gummas heal promptly under therapy with penicillin has been demonstrated by Tucker and Dexter.[187] Two patients are reported who received a total dose of 920,000 and 3,200,000 units of penicillin respectively, with dramatic alleviation of the acute symptoms and sustained subjective and objective improvement over observation periods of six hundred and eighty-six and four hundred and ninety-one days respectively. In neither case was a therapeutic paradox observed. These data suggest that penicillin is at least as effective in the treatment of visceral gummas as other forms of antisyphilitic treatment and offers the additional advantage of almost complete lack of toxicity, a factor of some importance when disease of the liver is present.

Some of the problems arising in the treatment of syphilis with penicillin are described by Hill.[188] Of considerable interest is the fact that this author has had the opportunity of examining "a patient with an extensive destructive gumma involving the center of the face, including the nasal septum, and the hard palate, who had received 2,400,000 Oxford units of penicillin before admission, without improvement. Therapy with induced malaria completely resolved the lesion." This is the first report of "resistance" to penicillin in benign late syphilis.

Penicillin in Cardiovascular Syphilis: Most syphilologists agree that specific therapy in cardiovascular syphilis favorably influences the course of the disease and increases life expectancy. The efficacy of penicillin in this condition cannot yet be assessed, since the drug has been used for far too short a period.

Russek and his associates[189] have treated 15 patients with cardiovascular syphilis, including 4 with aortic aneurysm, with penicillin in relatively large doses (40,000 units every two hours). Significant untoward reactions necessitating discontinuance of the use of the drug were not encountered. The rarity of Jarisch-Herxheimer reactions in cardiovascular syphilis was strikingly in contrast to their frequency among patients with early syphilis similarly treated. Four of the 15 patients in the present series showed distinct improvement in coronary reserve after treatment. The authors conclude that harmful reactions

187. Tucker, H. A., and Dexter, D. D.: Treatment of Gummatous Hepatic Syphilis with Penicillin, Arch. Int. Med. **78**:313 (Sept.) 1946.

188. Hill, W. R.: Problems Arising in the Treatment of Syphilis with Penicillin, New England J. Med. **235**:919 (Dec. 26) 1946.

189. Russek, H. I.; Cutler, J. C.; Fromer, S. A., and Zohman, B. L.: Treatment of Cardiovascular Syphilis with Penicillin, Ann. Int. Med. **25**:957 (Dec.) 1946.

to penicillin are uncommon in cardiovascular syphilis during the treatment in early post-treatment periods and that this form of therapy warrants further evaluation.

Penicillin in Neurosyphilis: Gammon, Stokes and their collaborators [190] report strikingly good results from therapy with penicillin alone in neurosyphilis and consider this "the first choice for the first treatment of neurosyphilis."

Their analysis of 161 patients with various manifestations of syphilis of the central nervous system indicates that the greatest effect on symptoms and signs occurred with respect to the psychoses, the incoordination, the tremors and the speech defects of dementia paralytica and the lightning pains of tabes dorsalis. Abnormalities of the spinal fluid responded dramatically. Within two years the spinal fluid in 62 per cent of their patients was normal or "near normal." In all types of neurosyphilis the outstanding therapeutic response was again in weight, usually accompanied with a sense of increased well-being.

In dementia paralytica, mental symptoms improved in 72 per cent of 47 patients, the most notable results being observed in those with severe symptoms of short duration. In juvenile paresis, improved mental status was noted less frequently. There were 40 patients with tabes or the tabetic form of dementia paralytica with lightning pains, and of these, 33 (82 per cent) were "improved." In the relief of tabetic pain, these authors believe that the effects of penicillin are "greater than might be expected as a result of spontaneous remission and on the whole compare favorably with results of other forms of therapy." In other symptoms of tabes no striking changes were noted. In meningovascular and asymptomatic neurosyphilis, the results were measured by the response of the spinal fluid. Fourteen patients had convulsions, a symptom which failed to improve notably after penicillin therapy.

The occurrence of neural Herxheimer reactions is recorded. Transient increases in mental abnormalities developed in 5 paretic patients; 4 with tabes dorsalis had exacerbation of their pains, and in 2 with syphilis of the spinal cord there developed transverse myelitis.

Koteen, Doty, Webster and McDermott [191] express the belief that "the penicillin therapy of neurosyphilis (exclusive of primary optic atrophy) approaches and may equal fever therapy in effectiveness." These investigators found that the administration of penicillin over a two week period produced a striking effect on abnormalities of the

190. Gammon, G. D.; Stokes, J. H., and others: Penicillin Therapy Alone in Neurosyphilis: An Analysis of Clinical Results, Ann. Int. Med. **25**:412 (Sept.) 1946.

191. Koteen, H.; Doty, E. J.; Webster, B., and McDermott, W.: Penicillin Therapy in Neurosyphilis, Am. J. Syph., Gonor. & Ven. Dis. **31**:1 (Jan.) 1947.

cerebrospinal fluid and on certain of the clinical manifestations of late neurosyphilis. They have treated with penicillin alone 111 patients with various forms of neurosyphilis. In 6 of 11 with dementia paralytica there were satisfactory remissions that have been sustained approximately two years. Forty-one patients with tabes dorsalis complained of a total of fifty-seven symptoms, subjective improvement in thirty-three of which was reported after penicillin therapy. There was no demonstrable correlation between the degree of abnormality of the cerebrospinal fluid and the symptomatic improvement. In a small number of patients with various clinical forms of meningovascular neurosyphilis the therapeutic results after penicillin were comparable to those usually observed after arsenotherapy. Striking improvement in the abnormalities present in the cerebrospinal fluid occurred both in patients with symptomatic and in those with asymptomatic neurosyphilis. The degree and rate of improvement were comparable to those previously observed after the use of fever therapy supplemented with metal chemotherapy. On the basis of their results, these authors state the belief that "the efficacy of the treatment is sufficiently close to the efficacy of fever to justify a trial of penicillin as the sole antisyphilitic therapy for patients with asymptomatic neurosyphilis, tabes dorsalis, and the various manifestations of meningovascular neurosyphilis." In dementia paralytica they also believe it justifiable to use penicillin first, giving additional treatment, preferably the induction of fever, promptly if significant improvement in the clinical signs and in the cerebrospinal fluid fails to appear within three months.

Heyman [192] has treated 141 patients with syphilis of the central nervous system with penicillin. His results are in general comparable to those reported by others. With the administration of 4,000,000 units of penicillin, "arrest" of the neurosyphilitic process was obtained in approximately 85 per cent of the cases. It is his belief that patients with early neurosyphilis respond more satisfactorily to penicillin than those whose disease is of longer standing, that the results in patients with maximal abnormalities of the cerebrospinal fluid in late syphilis are less satisfactory than the results in those with less significant abnormalities and that the early response of the spinal fluid is as good as that obtained from fever therapy with typhoid vaccine. Heyman recommends penicillin for the treatment of early neurosyphilis and late asymptomatic neurosyphilis provided adequate facilities for follow-up are available. He regards fever therapy as the treatment of choice in late asymptomatic neurosyphilis.

192. Heyman, A.: The Treatment of Syphilis of the Central Nervous System with Penicillin, Am. J. M. Sc. **213**:661 (June) 1947.

Penicillin in Asymptomatic Neurosyphilis: Moore and Mohr [193] have presented the detailed results of penicillin therapy in 48 patients with early asymptomatic neurosyphilis and in 43 with late asymptomatic neurosyphilis followed for more than three months after treatment. Pointing out that there are no valid data available on which to base a comparison with the results from no treatment whatsoever or from any previously available form of therapy, the authors state:

> At the moment, the most that can be said is that penicillin exerts a profoundly favorable effect on spinal fluid abnormalities in early and late asymptomatic neurosyphilis; that this effect is manifest, in order of promptitude and extent, on cell count, protein content, colloidal test, and, last of all, on the complement fixation (Wassermann) reaction; and that the speed and extent of the disappearance of all spinal fluid abnormalities is dependent upon the two factors of degree of these abnormalities before treatment and of the duration of syphilitic infection. Within the brief time limit of this study, and keeping in mind the small number of cases involved, spinal fluid normality, once achieved, seems usually to be stable.

They consider that in either early or late asymptomatic neurosyphilis the reappearance of increased cell count, increased protein or both is an indication for retreatment. They also suggest that it may be desirable to retreat patients in whom the Wassermann reaction of the spinal fluid remains positive, with little change from its original titer, for a year after the first course of penicillin therapy. Their personal preference for retreatment is the induction of fever and malaria in combination with the administration of penicillin.

Penicillin in Dementia Paralytica: Reynolds, Mohr and Moore [194] concur that in the treatment of dementia paralytica penicillin gives promise of becoming a valuable therapeutic adjunct. In their experience, however, the concurrent use of penicillin and malaria was productive of significantly better results than the use of penicillin alone. Forty-one patients with dementia paralytica were treated at the Johns Hopkins Hospital with commercial penicillin; 24 were treated with penicillin alone and 17 with penicillin and malarial therapy. Penicillin alone, in doses ranging from 2,000,000 to 10,000,000 units, produced at least some degree of clinical improvement in 11 of 24 patients (46 per cent). The response was better among patients whose symptoms were of recent onset. No patient whose symptoms had been present for a year or more prior to the institution of penicillin treatment showed any clinical improvement. Improvement in the abnormalities of the spinal fluid generally was apparent, although 3 patients showed persistent evidence of cerebrospinal fluid "activity." Penicillin administered

193. Moore, J. E., and Mohr, C. F.: Penicillin in the Treatment of Neurosyphilis: I. Asymptomatic Neurosyphilis, Am. J. Syph., Gonor. & Ven. Dis. **30**: 405 (Sept.) 1946.

194. Reynolds, F. W.; Mohr, C. F., and Moore, J. E.: Penicillin in the Treatment of Neurosyphilis: II. Dementia Paralytica, J. A. M. A. **131**:1255 (Aug. 17) 1946.

concurrently with malarial therapy resulted in clinical improvement in at least 10 of 17 patients (58 per cent). Improvement in the abnormalities of the spinal fluid was even more complete than when penicillin alone was given. There were no cases in which either the cell count or the total protein in the cerebrospinal fluid was abnormal for a period in excess of twenty weeks after therapy.

The effectiveness of concurrent penicillin-malaria therapy was such as to make it, in these authors' opinion, the treatment of choice for patients with dementia paralytica.

Seven patients with dementia paralytica were treated by Smith [195] with intramuscularly administered penicillin. No penicillin was found in the spinal fluid with the dosage employed. Of these patients, 4 made a "social recovery," 1 was improved, 1 was not improved and 1 died. Studies of the spinal fluid revealed improvements in both cell count and protein content; the reactions to colloidal gold and Wassermann tests remained abnormal longer.

Rose and Solomon [196] have utilized penicillin in a unique manner, namely, in combination with approximately one half the amount of fever therapy usually considered optimal. The clinical results in the first 100 patients who have been under observation for at least a year after this and other forms of therapy are described. The majority (75 per cent) of these patients had dementia paralytica. Fifty-two (69 per cent) were improved, 21 had shown no change and 2 were worse.

Penicillin in Abnormalities of the Cerebrospinal Fluid: The over-all early effects of administration of penicillin on the abnormalities of the cerebrospinal fluid in cases of symptomatic neurosyphilis have been described by Reynolds.[197] A total of 149 patients with various manifestations of late neurosyphilis (including tabes dorsalis, dementia paralytica, primary optic atrophy, meningovascular neurosyphilis and Erb's syphilitic spastic paraplegia) were treated with penicillin or with penicillin used in combination with malarial therapy. Improvement in the spinal fluid generally was apparent. As a rule, the cell count and protein content promptly became normal and remained so. The condition as revealed by the reactions to colloidal gold, mastic and Wassermann tests more gradually improved, the improvement usually being well sustained. The degree and rapidity of improvement in these patients with such diverse

195. Smith, R. H. F.: General Paresis of the Insane Treated with Penicillin, Lancet **1**:665 (May 17) 1947.

196. Rose, A. S., and Solomon, H. C.: Penicillin in the Treatment of Neurosyphilis: A Study of One Hundred Cases Followed Twelve Months or More, J. A. M. A. **133**:4 (Jan. 4) 1947.

197. Reynolds, F. W.: Penicillin in the Treatment of Neurosyphilis: IV. Cerebrospinal Fluid Changes in Cases of Symptomatic Neurosyphilis, Ann. Int. Med. **26**:393 (March) 1947.

manifestations of neurosyphilis could not definitely be correlated with the penicillin dosage, the duration of symptoms, or the extent of the abnormalities of the spinal fluid. The results following therapy with penicillin plus malaria were more favorable than those following treatment with penicillin alone.

Neural Reactions of the Jarisch-Herxheimer Type.—Reviewing the records of 208 patients with various forms of neurosyphilis treated with penicillin, Tucker and Robinson [198] report that some reaction to the initiation of treatment occurred in 54 patients (26 per cent). The majority of these reactions were febrile, but transitory mental confusion or agitation also occurred. In 2 patients receiving penicillin for dementia paralytica hallucinatory and paranoid trends became so extreme that it became necessary to commit both to institutional care. These authors report 2 additional patients with neurosyphilis in whom convulsions developed early in the course of penicillin therapy. The occurrence of these reactions within the first forty-eight hours of penicillin therapy and their association with a febrile response suggest that they were reactions of the Jarisch-Herxheimer type. It seems unlikely that they were due to a direct irritative action of penicillin, since the symptoms subsided spontaneously despite the fact that penicillin therapy was continued in undiminished doses.

Penicillin in Prenatal Syphilis.—In a study to determine whether penicillin crosses the placental barrier early in pregnancy, Woltz and Wiley [199] administered the drug preoperatively to 6 women for whom interruption of pregnancy was advised for therapeutic reasons. Penicillin was given either intravenously or intramuscularly, and at the time of operation specimens of maternal blood, amniotic fluid and fetal blood or tissue fluid were obtained. Their data reveal that (1) penicillin was found in the 10, 20, 21 and 25 week fetuses and that (2) penicillin was present in the amniotic fluid of the 12 week fetus after the administration of only 35,000 units to the mother.

Since arsenical drugs do not pass in high concentration to the fetal tissues prior to the latter half of pregnancy, the authors imply that penicillin may be the drug of choice in the prevention of congenital syphilis, especially when therapy is begun in early pregnancy.

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198. Tucker, H. A., and Robinson, R. C. V.: Neurosyphilitic Patients Treated with Penicillin: Probable Herxheimer Reactions, J. A. M. A. **132**:281 (Oct. 5) 1946.

199. Woltz, J. H. E., and Wiley, M. M.: The Transmission of Penicillin to the Previable Fetus: Its Significance in Prenatal Syphilis, J. A. M. A. **131**:969 (July 20) 1946.

Among a group of 730 patients with early syphilis treated with penicillin by Cole and his co-workers [200] there were 47 pregnant women. These authors concur in the belief that syphilis in pregnancy is an ideal situation in which to use penicillin because of the absence of severe reactions and because the drug may be used successfully even late in pregnancy provided the child is still viable. In their experience, there appeared to be no great danger of miscarriage or premature delivery, no evidence of damage to the unborn child, or, in contrast to intensive arsenotherapy, no danger of hemorrhagic encephalitis in the mother. Moreover, penicillin proved efficacious even when administered late in the course of pregnancy. There was 1 child with congenital syphilis, born of a mother who had received a total of but 300,000 units over a period of seven and one-half days (5,000 units every three hours). One other pregnancy terminated in stillbirth of a macerated fetus of 7 months, and although there were no clinical evidences of syphilis the authors interpret this as a therapeutic failure. There were two premature births, which are not attributed to penicillin therapy; in neither of the 2 children was syphilis known to develop. The authors stress the necessity of frequently repeated quantitative serologic tests in the management of the pregnant syphilitic woman and of her child.

Speiser and his co-workers [201] delineate the ideal form of antisyphilitic therapy in the pregnant woman as one which involves (1) freedom from serious toxic effects, (2) prevention of prenatal syphilis, (3) cure of the maternal infection, (4) cure of the congenitally syphilitic child in utero and (5) the completion of therapy within a short period. In their opinion, penicillin fulfils these requirements better than any drug previously employed. Among a series of two hundred and sixty-one pregnancies in 259 women, syphilis was proved to have developed in only 1.5 per cent of the infants. It is noted that prenatal syphilis may be prevented regardless of the period of gestation in which penicillin is started, that frequent observations of the mother during pregnancy are essential, that if a maternal clinical or serologic relapse occurs during the prenatal period retreatment may assure a nonsyphilitic child and that a patient who has responded satisfactorily after previous penicillin therapy need not be treated during a subsequent pregnancy provided adequate follow-up observations are assured.

From their studies involving three schedules of intensive antisyphilitic therapy in the prevention of prenatal syphilis, Olansky and Beck [202]

200. Cole, H. N.; Ayres, S., III; Barr, J. H.; Genatios, R.; Held, B.; Murphy, W. W.; Printz, D. R., and Strauch, J.: Use of Penicillin in the Treatment of Syphilis in Pregnancy, Arch. Dermat. & Syph. **54**:255 (Sept.) 1946.

201. Speiser, M.; Flaum, G.; Moon-Adams, D., and Thomas, E. W.: Penicillin Therapy for Syphilis in Pregnancy, J. Ven. Dis. Inform. **28**:108 (June) 1947.

202. Olansky, S., and Beck, R.: Rapid Treatment of Prenatal Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **31**:51 (Jan.) 1947.

deduce that intensive treatment offers the best outlook for a nonsyphilitic child. One hundred and forty-seven patients were treated, 74 by five or seven day schedules of arsenobismuth therapy, 24 by the use of penicillin alone and 49 with combinations of oxophenarsine hydrochloride, bismuth and penicillin. The pregnancies resulted in 128 live births. Eleven terminated in abortions or stillbirths, an incidence considered to be no greater than that in a similar, nonsyphilitic group. Nine of the patients became pregnant again but received no antisyphilitic therapy during the second pregnancy. Despite the fact that 64 of the women were treated during the last trimester of pregnancy, syphilis developed in only 1 infant; the mother had been treated with penicillin and metal chemotherapy. The incidence of untoward reactions with all three regimens was low, particularly with the schedules employing penicillin alone and penicillin oxophenarsine hydrochloride and bismuth in combination. The authors stress that quantitative serologic tests for syphilis and careful physical examinations be performed monthly during pregnancy so that in the event of reinfection or relapse retreatment may be instituted in time to prevent congenital syphilis.

Penicillin in the Treatment of Syphilis in Children.—Yampolsky and Heyman [203] have used penicillin in the treatment of 61 children with various manifestations of syphilis. Included in their series were 32 infants, and satisfactory results were obtained in 23 of them. An immediate clinical response was observed in all patients, and healing of cutaneous and mucosal lesions often occurred by the end of the course of treatment. Osseous lesions also showed prompt improvement, but complete resolution usually did not occur for two or three months. Of 9 patients in whom treatment was considered to have failed, there were 4 clinically well but seroresistant, 2 clinically worse with associated serologic relapses and 3 who died. None of the deaths was thought to be due to penicillin.

The majority of patients with interstitial keratitis did not improve satisfactorily with parenterally administered penicillin, which also was of little value in the treatment of Clutton's arthritis. The changes in the cerebrospinal fluid in late congenital asymptomatic neurosyphilis were in general satisfactory and comparable to those obtained with fever therapy. Little or no clinical improvement was noted in juvenile paresis treated with penicillin. One patient with mild nerve deafness had improved hearing, and another with severe deafness showed no improvement after receiving penicillin therapy.

In general, the results obtained with penicillin in the treatment of syphilis in children seemed to depend on the nature and duration of the disease. Although effective in the treatment of infantile congenital

203. Yampolsky, J., and Heyman, A.: Penicillin in the Treatment of Syphilis in Children, J. A. M. A. **132**:368 (Oct. 19) 1946.

syphilis and in early neurosyphilis, penicillin appeared of little or no value in the treatment of the late manifestations of the disease.

Rose, György and Ingraham [204] report that further experience with penicillin in the treatment of syphilitic infants confirms their earlier impression that penicillin sodium given by repeated intramuscular injections is a satisfactory therapy for the congenitally infected syphilitic infant. They now have treated 36 infants with congenital syphilis with intramuscular injections of penicillin in doses ranging from 11,000 to 75,000 units per pound of body weight over periods of seven to fifteen days. Nineteen have become clinically well and seronegative, 6 have become clinically well but remain seropositive and 3 were still seropositive when the follow-up study was interrupted. Two were clinically well but had doubtful reactions to serologic tests for syphilis, 7 died, none as a direct result of penicillin therapy, and 4 have been treated too recently to evaluate beyond the prompt clinical improvement. There was no instance of serologic relapse and only one clinical relapse. These authors recommended that the total dosage of penicillin sodium be not less than 75,000 units per pound of body weight and that the course of therapy be not less than fifteen days. They find no necessity for low initial dosage and recommend early hospitalization, with vigilant pediatric supervision.

Observations incident to the treatment of 252 infants with early congenital syphilis by the use of penicillin have been recorded by Platou and his co-workers, representing five cooperating university clinics.[205] A single course of penicillin administered over a period of seven and one-half to fifteen days yielded satisfactory results in 73 per cent of the infants and unsatisfactory results in 9.1 per cent, while in 17.9 per cent the results are classified as uncertain. Dosage schedules employing more than 40,000 units of the drug per kilogram of body weight yielded better results than those utilizing lesser amounts. Most babies became seronegative between the fourth and twelfth months after therapy, but serologic reversal was not unusual after this period had elapsed. It is recommended that infants with syphilis be given a total dosage of at least 100,000 units per kilogram of body weight and that this amount be divided into approximately one hundred and twenty intramuscular injections, given every three hours over a period of twelve to fifteen days.

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204. Rose, E. K.; György, P., and Ingraham, N. R., Jr.: Penicillin in the Treatment of the Syphilitic Infant: A Progress Report, J. Pediat. **29**:567 (Nov.) 1946.

205. Platou, R. V.; Hill, A. J., Jr.; Ingraham, N. R.; Goodwin, M. S.; Wilkinson, E. E.; Hansen, A. E., and Heyman, A.: Early Congenital Syphilis: Treatment of Two Hundred and Fifty-Two Patients with Penicillin, J. A. M. A. **133**:10 (Jan. 4) 1947.

Further observations on the use of penicillin in the treatment of infantile congenital syphilis have been reported by the university groups at New Orleans, Philadelphia, Baltimore and Galveston.[206] Reactions in children to penicillin therapy have been inconsequential, and deaths occurring among the combined series of 191 infants could in no instance be related to the use of penicillin. The percentage of treated infants in whom seronegativity developed increased with each month of observation for at least eighteen months.

Wyvell,[207] reporting the results of penicillin treatment of 40 patients with congenital syphilis, finds the drug valuable in neonatal syphilis and in syphilis acquired in childhood. Her results with congenital syphilis in older children were less favorable; in 7 who had involvement of the central nervous system the outcome was "not very encouraging."

Hill, Platou and Komentani [208] properly point out that until the spontaneous evolution of a self-limited process is known it is impossible to assess the worth of any form of therapy intended to ameliorate the process. They have considered osseous congenital syphilis in relation to the effects of penicillin on the rate of healing in this light. These investigators' study indicates that:

1. The behavior of osseous congenital syphilis in untreated infants follows a fairly definite pattern of rapidly increasing severity during the first 3 months of life and slow healing thereafter. Improvement results from decreasing severity of osteomyelitis and osteochondritis; periosteal changes increase in prominence over a longer period and persist as the commonest residua. The course of a given lesion in any individual patient cannot be accurately predicted.

2. Dosages of penicillin employed so far have temporarily accelerated healing of osseous syphilis only in infants treated during the first three months of life. This acceleration, as in untreated controls, occurs principally in osteochondritis and osteomyelitis; simultaneous improvement in periostitis is only of probable significance. No such significant effects were observed among those treated during the next four months. The mode of healing for any particular type of lesion, as herein described, has not been evaluated.

3. Increase in severity of these lesions during or shortly after penicillin therapy occurs in an age group where this phenomenon is to be expected without treatment.

4. Pseudoparalysis disappears without any specific changes in the roentgenograms; indeed, osseous lesions may even appear worse after pseudo-paralysis subsides.

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206. Platou, R. V.; Hill, A. J., Jr.; Ingraham, N. R.; Goodwin, M. S.; Wilkinson, E. E., and Hansen, A. E.: Effect of Penicillin in the Treatment of Infantile Congenital Syphilis: Further Observations, Am. J. Dis. Child. **72**:635 (Dec.) 1946.

207. Wyvell, D. B.: Penicillin Therapy in Congenital Syphilis, Texas State J. Med. **42**:578 (Feb.) 1947.

208. Hill, A. J.; Platou, R. V., and Komentani, J. T.: Osseous Congenital Syphilis: Effects of Penicillin on Rate of Healing, J. Pediat. **30**:547 (May) 1947.

(To Be Concluded)

Book Reviews

Heparin in the Treatment of Thrombosis. By J. Erik Jorpes. Second edition. Price, $6.50. Pp. 260, with 21 illustrations, 2 in color. New York: Oxford University Press, 1947.

This monograph presents the results of a comprehensive study of the anticoagulants, emphasizing their development, chemistry and clinical uses. It is written by a member of the Swedish school who is particularly interested in and has done much to develop heparin as a clinical agent and is, to that extent, biased.

The chemical researches which are necessarily included for the sake of completeness are perhaps too technical for the average physician but serve nicely to illustrate the methods of research necessary to isolate and define compounds of therapeutic value. This would seem to be timely in view of the increasing number and importance of specific chemical agents.

The clinical efficacy of heparin has been thoroughly evaluated in a large series of cases. Results, which seem to be valid, are certainly exciting and warrant much more clinical trial. Several important points are brought out which have not been emphasized in our literature. For example, there is the claim, on apparently good clinical basis, that heparin is useful therapeutically in thromboembolic states for its thrombolytic action as well as useful prophylactically. The author suggests the use of the drug over long periods of time, with gradually decreasing dosage as improvement progresses, and many failures have been attributed to the sudden and premature cessation of therapy. It is interesting to find that in large autopsy series thromboembolic phenomena are at least as common in medical cases as they are in surgical cases

Dangers of the use of heparin are minimized, and the intravenous use of protamine sulfate for the instantaneous reversal of its action is emphasized.

The author discusses "dicumarol," apparently only to condemn its use. The objection to this drug and the firm stand for heparin have much basis in fact, but further trial and more clinical experience seem necessary before one may pass on the relative merits of the two drugs. The statement in the preface that "heparin is as specific in thrombosis as insulin is in diabetes" may not be entirely correct, but the subject certainly shows a great deal of promise.

This volume constitutes an excellent introduction for the discriminating reader.

Cushny's Pharmacology and Therapeutics. Revised by Arthur Grollman and Donald Slaughter. Thirteenth edition. Price, $8.50. Pp. 868, with 74 illustrations. Philadelphia: Lea & Febiger, 1947.

In its present form, this standard work, now in its thirteenth edition, continues to justify its reputation as a ". . . severely critical, rigorously scientific, general textbook written by an experimental pharmacologist." To this statement it should be added that the present editors contribute to the background of the book the further qualifications of a well known pharmacologist and internist.

More specifically, this book is recommended especially by its combination of reasonable size with completeness; it never leads the reader into purely speculative matters, and yet the entire field of modern pharmacology is amply covered. Emphasis is placed on the practical application of the subject to practical therapeu-

tics, a fact which should appeal to the busy physician as well as to the harassed medical student. No attempt is made to include the exhaustive detail of a compendium.

An introductory section of forty pages is valuable for its concise discussion of the principles of pharmacodynamics and of pharmacopeias and biologic assay. The body of the book considers in succession various groups of drugs which have been classified in the ways that have seemed most logical for each group. Thus, the inorganic substances are considered together, as are substances characterized chiefly by local action, those characterized by action after absorption, anthelmintics, antiseptics and disinfectants and vaccines, serums and miscellaneous biologic preparations. Several drugs, such as the newer sulfonamide compounds, the antibiotics and folic acid, make their first appearance in a textbook of pharmacology.

An additional classification is appended which groups all the drugs previously considered according to their therapeutic uses and which would seem especially valuable from the purely practical standpoint.

Penicillin Therapy Including Streptomycin, Tyrothricin and Other Antibiotic Therapy. By John A. Kolmer, M.D. Second edition. Price, $6.00. Pp. 339, with 27 illustrations. New York: D. Appleton-Century Company, Inc., 1947.

The appearance of the second edition of this book two years after that of the first is rather definite proof that there was need of such a textbook and that there is a real necessity to record promptly the newer studies of antibiotics, a subject which is going ahead by leaps and bounds. Because of all the new material that has appeared in the last two years, Kolmer has been obliged to rewrite completely the second edition. He has also incorporated a considerable number of additional illustrations. Even with the many changes that have been necessary to bring the new edition up to date at the time of publication, it is almost impossible really to keep a book au courant with the studies that are appearing almost daily in the field of antibiotic therapy. Bacitracin is an excellent example. Kolmer has two paragraphs on this particular new antibiotic substance, which gives promise of being extremely important in the future and which will require pages in the third edition of the book when and if it appears. A long chapter is devoted to penicillin in the treatment of syphilis, but little is said about the failure of this drug to be always satisfactory, probably because at the time of publication the reports of failure had not yet started to come in.

These criticisms are not truly critical but are made merely to illustrate the difficulties of keeping a book up to the minute on a subject which is so mutable. The advice and information that Kolmer gives on how properly to use antibiotics are excellent. The book may be used by physicians with the confidence that the information on what is known at the time of its appearance is authentic and detailed. It can be recommended highly to every type of specialist who is dealing with certain infections, from those of the eye to those of the genitals.

Milk and Food Sanitation Practice. By H. S. Adams, B.Sc. Price, $3.25. New York: The Commonwealth Fund, 1947.

This book fills an important need in the field of public health by presenting in a clear and well organized manner the present concepts of the principles of milk and food sanitation and how these principles may be put into practice. The author points out the usual problems encountered in the field of milk and food sanitation and then proceeds to describe in concise and not too technical language the methods

and procedures which have proved of greatest use in meeting these situations. The style of presentation and the practical manner in which the subject is handled make the book especially valuable to public health engineers and sanitarians in their work in the field.

The first part is devoted to various aspects of milk sanitation. In this section one finds excellent discussions on the essentials of the sanitary production of milk and on many of the problems connected with pasteurization. Attention is also given to laboratory procedures used to evaluate a milk supply and the sanitary control of frozen dessert. The chapter dealing with the planning and administering of a milk control program is full of useful suggestions for any one interested in the field of public health administration.

Problems of food sanitation and control are discussed in the second section. Following the trend of modern concepts of public health, the author emphasizes the educational approach in coping with problems of food handlers.

The usefulness of this book is enhanced by a number of appropriate appendixes, which contain a wealth of practical information pertinent to the field activities of personnel dealing with milk and food sanitation. The simple style and presentation make it a valuable reference for any one interested.

Paravertebral Block in Diagnosis, Prognosis and Therapy. By Felix Mandl, M.D. Translated by Gertrude Kallner. Price, $6.50. New York: Grune & Stratton, Inc., 1947.

Paravertebral block used to be thought of as belonging to the domain of the vascular surgeon, who would use it as a preoperative test for sympathectomies or employ it for the relief of vasospastic disturbance occurring during the acute vascular occlusions. Professor Mandl has long been a student in this field; in fact, he published a little known monograph on this subject twenty-five years ago. The present volume is a greatly extended body of observations, gathered under difficult conditions in Vienna and later in Jerusalem.

The internist will be greatly interested in the use of this method as a differential diagnostic procedure in painful visceral conditions. More than that, the method has therapeutic value, since single or repeated injections of procaine hydrochloride into the appropriate sympathetic ganglions are described to have value. The chapters on the results of paravertebral injections in angina pectoris, paroxysmal tachycardia and essential hypertension are especially stimulating.

This is a valuable contribution on temporary block of the sympathetic ganglions. There is no field of medicine in which it could not be profitably applied. The translation is smooth and rapidly understood but needs more close editing. The illustrations are simple and diagrammatic.

Significance of the Extracellular Fluid in Clinical Medicine. By L. H. Newburgh, M.D. Price, $1.80. Pp. 64. Ann Arbor, Mich.: J. W. Edwards, Inc., 1946.

The author of this monograph is well qualified to write on the significance of extracellular fluids in clinical medicine, as he has spent many years investigating certain phases of the subject. He has accomplished the difficult task of translating information of a highly technical nature into language understood by most clinicians.

The first part of the monograph is taken up with the physiology of extracellular fluids, and the nature of the regulatory mechanisms is outlined in a simple but emphatic manner. The second portion is concerned with the clinical significance of the abnormalities which occur in the extracellular fluid system. The author first familiarizes the reader with the features of the extracellular fluid in its normal

state and then discusses the relations between abnormalities of this fluid and a number of diseases.

After the reader understands the nature of the extracellular fluid and its regulation by the kidneys, he is prepared to evaluate the clinical significance of abnormalities in this system.

La réticulose histiomonocytaire. By P. Cazal. Price, 350 francs. Pp. 196. Paris: Masson & Cie. 1946.

This is an extremely difficult book to review. It is on a subject which is comparatively new. In the English language, the terminology employed by pathologists differs from person to person, and many of the papers written in English are difficult to understand for that reason. When a subject is written in French, it can be readily appreciated that the reader is going to have a great deal of trouble in interpreting the French nomenclature, translating it into English and then in turn transferring the English nouns to the terms that the pathologist is accustomed to use.

Undoubtedly the monograph will be of considerable value to one who is interested in the subject matter treated by Dr. Cazal, but most pathologists will probably find that the book is not of practical value to them, and clinicians will discover that they probably will not be able to make use of it at all.

Die hormonalen Aspekte des Fortpflanzungsprozesses. By Jules Samuels, M.D. Pp. 152. Amsterdam, Holland: Holdert & Company, 1947.

This monograph reviews present concepts of the interrelationship of various hormones in the process of fertilization. The gist of it is summarized in English, French and Dutch as well as German—a helpful gesture to those unfamiliar with the last language, which is used for the body of the text. An excellent bibliography appears at the end.

On the whole, the work is useful for reference. It will interest a limited number of readers. Students in the field, however, will appreciate the manner in which the author has brought together varying views on a complicated phase of endocrinology.

Health Instruction Yearbook, 1946. Compiled by Oliver E. Byrd. Price, $3. Pp. 399. Stanford University, Calif.: Stanford University Press, 1946.

This fourth edition of the "Health Instruction Yearbook" is a summary complete with bibliographic references to three hundred and eighty-four of the most recent articles appearing in various scientific, medical, statistical and public health journals, including *The Journal of the American Medical Association* and the *American Journal of Public Health.*

It includes a new chapter on international health compatible with awakened American participation in world affairs and with the fact that major health problems are not restricted by geographic or international boundaries.

This book achieves its purpose well in that it contains a wealth of the latest and most reliable health facts essential to all public health personnel, educators, librarians and statisticians, as well as helping those interested to keep abreast of recent advances in the mounting mass of scientific literature. It does not contain the detailed medical information sought by practicing physicians or medical researchers.

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